

# Background Document on Gulf War-Related Research for The Health Impact of Chemical Exposures During the Gulf War: A Research Planning Conference

February 28 - March 2, 1999  
Atlanta, Georgia

*Sponsored by*  
**Centers for Disease Control and Prevention**

in coordination with  
the Office of Public Health and Science (Department of Health and Human Services),  
the National Institutes of Health, and  
the Agency for Toxic Substances and Disease Registry

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## List of Acronyms and Abbreviations

ANG	Air National Guard
ATSDR	Agency for Toxic Substances and Disease Registry
CARC	Chemical Agent Resistant Coating
CCEP	Comprehensive Clinical Evaluation Program
CDC	Centers for Disease Control and Prevention
CIA	Central Intelligence Agency
DHHS	Department of Health and Human Services
DoD	Department of Defense
DSB	Defense Science Board
DU	Depleted Uranium
DVA	Department of Veterans' Affairs
EMG	electromyography
FDA	Food and Drug Administration
GAO	Government Accounting Office
ICD-9	International Classification of Diseases, Ninth Revision
IOM	Institute of Medicine
MCS	Multiple Chemical Sensitivity
MMPI	Minnesota Multiphasic Personality Inventory
NIH	National Institutes of Health
PAC	Presidential Advisory Committee on Gulf War Veterans' Illnesses
PAH	Polycyclic Aromatic Hydrocarbon
PGHR	Persian Gulf Health Registry
PGVCB	Persian Gulf Veterans Coordinating Board
PL	Public Law
PSOB	Presidential Special Oversight Board
RR	rate ratio or relative risk
RWG	Research Working Group
SIU	Special Investigation Unit on Gulf War Illness
SMR	Standardized Mortality Ratios
U.K.	United Kingdom
U.S.	United States
USAEHA	U.S. Army Environmental Hygiene Agency
VA	Veterans' Administration
VOC	Volatile Organic Compound

## EXECUTIVE SUMMARY

The purpose of this document is to provide background information to participants in the upcoming conference, *The Health Impact of Chemical Exposures During the Gulf War: A Research Planning Conference*, sponsored by the Centers for Disease Control and Prevention in coordination with the Office of Public Health and Science (Department of Health and Human Services), the National Institutes of Health, and the Agency for Toxic Substances and Disease Registry. In response to U.S. House of Representatives Report 105-205, the conference is to be held on February 28-March 2, 1999 in Atlanta, Georgia for the purpose of obtaining broad public input into the development of a multi-year research plan investigating the relationships of chemical exposures to illnesses among Gulf War veterans.

The 697,000 men and women of U.S. military services who served in the Gulf region in 1990 and 1991 were exposed to a wide array of known and potential hazards to health including blowing dust and sand particles, smoke from oil well fires, petroleum fuels and their combustion products, possible exposure to chemical warfare nerve agents and biological warfare agents, pyridostigmine bromide pills to protect against organophosphate nerve agents, insecticides, vaccinations, infectious diseases, depleted uranium, and psychological and physiological stress. Quantitative data for exposure of soldiers to most of these agents during Gulf deployment, however, are not available. Appendix A of this document gives an account of events related to health concerns of Gulf War veterans. Appendix B discusses what is known concerning exposures and potential health consequences of the most likely health risk factors associated with the Gulf War experience.

Gulf War veterans registered in the U.S. Department of Defense's Comprehensive Clinical Evaluation Program, the U.S. Department of Veterans' Affairs Persian Gulf Health Registry, and the United Kingdom Ministry of Defence Medical Assessment Programme show an array of health symptoms and a distribution of disease diagnoses involving a wide variety of organ systems. In these programs, clinicians were unable to assign a standard diagnostic disease category to about 20-30% of participants other than *symptoms, signs and ill-defined conditions*. Three diagnostic disease categories (*psychological conditions, musculoskeletal diseases, and symptoms, signs and ill-defined conditions*) represented more than 50% of the primary diagnoses. The overall symptom pattern for Gulf War veterans in the clinical programs has been noted to be consistent with experiences of U.S. veterans of previous wars.

Various review panels and groups have evaluated information regarding illnesses among Gulf War veterans within the past 4-5 years. Appendix A summarizes recommendations from many of these review panels. Given the broad range of illnesses and health symptoms noted among Gulf War veterans and the lack of exposure data, these groups generally have concurred that no single cause of the multiple illnesses could be established. These groups have made several recommendations for research including: 1) epidemiological research to compare prevalence rates of illnesses in Gulf War veterans with appropriate control populations; 2) in-depth neurophysiological, neuropsychological, and psychological evaluations comparing symptomatic

and asymptomatic Gulf War veterans; 3) research on health effects from specific risk factors such as stress, pesticides, depleted uranium, pyridostigmine bromide, and low-level exposure to chemical warfare nerve agents; 4) research on health effects from mixtures of chemicals (e.g., pesticides, pyridostigmine bromide, and chemical warfare nerve agents) alone and in combination with other risk factors; 5) epidemiological research on the health status of U.S. troops known to be in the vicinity of an Iraqi weapons storage site, near Khamisiyah, Iraq, in March 1991 when low-level exposure to sarin and cyclosarin may have occurred compared with troops outside of the area; and 6) research into the causes, methods of prevention, and methods of treatment for musculoskeletal conditions and stress-related disorders.

The U.S.-government sponsored research projects which are coordinated by the Research Working Group of the Persian Gulf Veterans Coordinating Board address a wide spectrum of basic and applied topics related to illnesses among Gulf War veterans. Appendix C describes and evaluates selected published studies related to health concerns of Gulf War veterans. Appendix D contains descriptions of ongoing research projects related to: 1) multiple symptom disorders; 2) genetic differences in susceptibility to chemicals; 3) health effects from mixtures of chemicals and other risk factors; 4) treatment of chronic multiple symptom disorders in Gulf War veterans; 5) health effects from low-level, subclinical exposures to chemical warfare nerve agents; 6) health effects from pyridostigmine bromide; 7) assessment and definition of Gulf War illnesses; 8) prevalence of illnesses and associations between chemical exposures and illnesses in Gulf War veterans; and 9) health effects from depleted uranium exposure.

Published epidemiological studies of mortality rates, rates of hospitalizations, and rates of birth defects after the Gulf War have not found consistent, statistically significant differences between active-duty U.S. military personnel who were deployed to the Gulf War compared with active-duty personnel who were not deployed to the Gulf, except for a higher rate of mortality from unintentional injuries (such as automobile accidents). Further epidemiological research efforts are ongoing to track mortality, hospitalization, and reproductive outcome among groups of Gulf-deployed veterans and non-deployed veterans of the same era.

In contrast to the hospitalization and mortality studies, numerous epidemiological studies of self-reported health symptoms consistently have found statistically significantly higher rates of self-reported symptoms in groups of Gulf-deployed compared with non-deployed veterans and provide evidence that there may be an increased frequency of chronic, multi-systemic conditions of ill health among groups of Gulf War veterans. The array of reported symptoms are, in general, difficult to diagnose into a disease category. The most frequently reported symptoms are similar to the most frequently reported symptoms among veterans diagnosed as having *symptoms, signs and ill-defined conditions* in the previously discussed clinical programs (fatigue, headache, memory problems, sleep disturbances, skin rash, joint or muscle pain, and shortness of breath) and appear to overlap with several of the symptoms in other symptom-based disorders including chronic fatigue syndrome, fibromyalgia, and multiple chemical sensitivity. Using a mathematical technique called factor analysis to examine associations among symptoms reported in groups of Gulf War veterans, one group of investigators proposed that there might be unique health

disorders among Gulf War veterans, whereas two other groups of investigators reported finding no evidence of a unique disorder among Gulf War veterans when control groups were included in the analysis.

The lack of exposure data makes it difficult, if not impossible, to know the cause of many of the illnesses among Gulf War veterans. In attempts to obtain clues to possible causes, however, several epidemiological studies are looking for associations between self-reported symptoms and self-reported Gulf War experiences and exposures. To date, a few published studies, mostly of a small scale, have reported some associations between self-reported symptoms and particular risk factors (e.g., receiving multiple vaccinations, exposure to pesticides or debris from Scud missiles), but results are not consistent across studies. Several planned and ongoing research projects are similarly designed to look for possible associations between health symptoms and self-reported exposure to risk factors, including the large-scale Veterans' Administration (VA) National Health Survey. Other ongoing projects are taking a different approach to searching for etiological clues by comparing hospitalization rates, self-reported symptoms, and/or clinical measurements of neurophysiological and neuropsychological variables in various groups of veterans known to be at different geographical locations in March 1991 when low-level exposure to nerve agents may have occurred near the Iraqi weapon storage site near Khamisiyah.

Several hypotheses concerning the cause of difficult-to-diagnose illnesses among some Gulf War veterans remain plausible: some investigators hypothesize physiological changes that are stress-induced; some hypothesize causative relationships to low-level exposure to neurotoxic chemicals; and others hypothesize causative interactions between stress and low-level exposure to mixtures of chemicals. Limited suggestive evidence from a few published animal studies has led some to suggest that delayed neurological effects may occur from short-term exposure to mixtures of anti-cholinesterase agents that may have additive or synergistic effects. To date, the relevance of these animal studies to possible chronic neurological impairment in Gulf War veterans is uncertain for several reasons including the high exposure levels to which the animals were exposed and other potential differences between mixtures to which the animals were exposed and mixtures that may have been experienced by soldiers in the Gulf region. Short-term, high-level exposure to certain carbamate and organophosphate nerve agents is known to produce delayed neurological effects in animals and humans, but the occurrence of delayed effects from short-term, low-level exposure to these types of chemicals (an exposure scenario presumed to be relevant to the Gulf War experience of some veterans) is uncertain. Ongoing research projects at several institutions are evaluating possible delayed effects on neuropathological, neurobehavioral, and immunological variables in several animal species exposed to low-levels of various mixtures of cholinesterase-inhibiting chemicals (e.g., sarin, insecticides, and pyridostigmine), alone and in combination with other risk factors such as stress and vaccinations.

Ongoing basic research projects at several institutions are examining hypotheses related to the biochemical and/or genetic basis for differences among individuals in susceptibility to neurotoxic, cholinesterase-inhibiting chemicals such as organophosphate chemical warfare nerve agents (e.g., sarin) and carbamate anti-nerve-agent drugs (e.g., pyridostigmine bromide). Results from these

projects may lead to new methods to identify individuals at greater risk for neurological effects from cholinesterase-inhibiting chemicals or new prophylactic methods against neurological effects from chemical warfare nerve agents.

Several studies have evaluated neurophysiological and neuropsychological variables in small groups of symptomatic Gulf War veterans, but, in general, have not found obvious or consistent changes. Some of the studies, however, have found subtle changes in several variables in some of the examined patients. Ongoing research projects at numerous institutions are examining a wide range of clinical and laboratory physiological variables in attempts to identify objective diagnostic variables that may be consistently affected in Gulf War veterans experiencing multiple chronic symptoms. Endpoints being evaluated include: brain activation patterns determined with magnetic resonance imaging; nerve firing rate of the peroneal nerve; quantitative electroencephalographic pattern analysis; changes in neurohormonal levels in response to different stressors; cerebral spinal fluid levels of neurotransmitters; pain threshold measurements; esophageal smooth muscle motility; viral infections; immune function; and various physiological responses (e.g., blood pressure, heart rate, eyeblink) to acute physical, chemical, or cognitive challenges. In general, it is believed that this body of research may lead to a better basis for proposing new methods of diagnosis and treatment for Gulf War veterans with multiple unexplained chronic symptoms including fatigue, headache, muscle and joint pain, and chemical sensitivities.

In response to the wide diversity of illnesses and symptoms experienced by Gulf War veterans and the uncertainty of their cause, several reviewers have noted that treatment should proceed on an individual basis. Treatment is best addressed when objective clinical measures of distinct illness can be made, but, in the absence of such measures, multidisciplinary treatment of symptoms may be effective (involving medical evaluations, exercise programs, various therapy programs, and counseling). The U.S. Department of Defense has a Specialized Care Program using such an approach for Gulf War veterans with persistent, non-specific symptoms, and, in collaboration with the Department of Veterans' Affairs, has established a 2-year, multiple-site, control trial of cognitive behavioral therapy, aerobic exercise programs, and usual and customary care for such patients. Two other ongoing treatment trials are based on limited evidence suggesting that some Gulf War veterans with non-specific, chronic symptoms may be infected with microorganisms that are difficult to detect. These are double-blind clinical trials of long-term antibiotic treatment; one with symptomatic patients with positive findings for mycoplasma infection and the other with symptomatic patients with bacterial remnants in their urine.

During the upcoming two-and-a-half day conference, participants from various disciplines will meet several times in Workgroups with the goal of discussing and recommending further research in one of four focus areas related to illnesses among Gulf War veterans:

- 1) Pathophysiology, Etiology, and Mechanisms of Action;
- 2) Assessment and Diagnosis;
- 3) Treatment; and
- 4) Prevention.

Final reports and recommendations from each Workgroup will be presented to the conference at large prior to adjournment.



## 1. Purpose of the Conference

The current conference, *The Health Impact of Chemical Exposures During the Gulf War: A Research Planning Conference*, is convened, under the support specified by House Report 105-205<sup>1</sup>, to obtain broad public input into the development of a multi-year research plan investigating relationships of chemical exposures to illnesses among Gulf War veterans (Eisenberg, 1998).

House Report 105-205 provided funding to the Office of the Secretary, Department of Health and Human Services (DHHS) to support research in the areas of:

- C “multiple chemical sensitivity”;
- C “genetic differences in the ability to metabolize environmental agents commonly encountered during the Persian Gulf”;
- C “how multiple exposures of chemicals interact to exert their toxicity on an organism”; and
- C “treatment protocols which are being developed in the public and private sectors for illnesses resulting from chemical and other environmental exposures” (Eisenberg, 1998).

The plan is to be developed without duplicating existing research efforts contained within the research plans of the Research Working Group (RWG) of the Persian Gulf Veterans Coordinating Board (PGVCB) (Eisenberg, 1998).

## 2. The Gulf War: Overview

Shortly after Iraqi armed forces invaded Kuwait on August 2, 1990, Coalition troops (i.e., troops from the United States [U.S.], United Kingdom [U.K.], Canada, France, Saudi Arabia, Egypt, Syria and other countries) began deployment in Operation Desert Shield. Within two months, 200,000 U.S. troops had been added to those already in the Gulf area. Beginning on January 16, 1991, air attacks against the Iraqi army opened the phase of operations known as Operation Desert Storm (IOM, 1996b). The first oil well fires were started in Kuwait by the Iraqis on January 20, 1991 and the majority of oil well fires had been started by February 19, 1991 (Spektor, 1998; DoD, 1998e; PAC, 1996b). By February, 1991, more than 500,000 U.S. troops were in the field facing the Iraqi armed forces. Operation Desert Storm ended after a brief ground war from February 24 to February 28. U.S. troops were removed quickly from the area, and by June, 1991, fewer than 50,000 U.S. troops remained. A total of approximately 697,000 U.S. military men and women served in Operations Desert Shield and Desert Storm in 1990 and 1991 (Joseph et al., 1997). During the war, deaths among U.S. troops were restricted to 148 combat deaths and 145 deaths due to disease or unintentional injuries; only 467 additional individuals among U.S. troops sustained injuries (PAC, 1996b). It was well known that Iraq had chemical and biological warfare capabilities, but several review panels have concluded that there is no convincing evidence that Iraq used chemical or biological warfare agents against U.S. troops (DSB, 1994; NIH, 1994a,b; IOM, 1996b; PAC, 1996a,b; 1997; see Appendix A: *Account of Events Related to Health Concerns of Gulf War Veterans*). The Department of Defense (DoD)

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<sup>1</sup> House Report 105-205 accompanied the 1998 U.S. House of Representatives Appropriations Bill for the Departments of Labor, Health and Human Services, and Education and Related Agencies.

released information in June 1996 that, in March 1991, U.S. forces demolished Iraqi weapon-storage sites in the Khamisiyah region. After the demolition, the sites were determined to have contained chemical warfare agents (e.g., the nerve agents, sarin and cyclosarin), thus indicating the possibility that certain U.S. troops may have been exposed for short periods of time to low levels of nerve agents (see Appendix B: *Exposure to Chemicals During the Gulf War*).

Upon return from the Gulf War, some U.S. veterans reported an array of general symptoms of ill health including fatigue, skin rash, headache, muscle and joint pain, memory disturbance, concentration difficulties and memory loss, shortness of breath, sleep disturbances, and diarrhea. Health concerns among some veterans still persist in 1999.

Various review panels have concluded that no single cause has been established for these symptoms of ill health (DSB, 1994; NIH, 1994a,b; IOM, 1996b; PAC, 1996a,b; 1997; U.S. Senate, 1998), but several potential explanations have been proposed including: possible exposure to low levels of chemical or biological warfare agents; use of pyridostigmine bromide pills to protect against chemical warfare nerve agents; exposure to airborne sand particles and/or oil-well fire smoke; exposure to mixtures of pesticides, insect repellents, and other chemicals; anthrax and botulinum toxoid vaccines; infectious diseases; depleted uranium; and physiological and psychological stress (see Appendix B: *Exposure to Chemicals During the Gulf War* for more details).

### **3. Illnesses Among Gulf War Veterans**

#### ***The Department of Veterans' Affairs Persian Gulf Health Registry and the Department of Defense Comprehensive Clinical Evaluation Program***

Health registries for U.S. Gulf War veterans were established in 1992 by the Department of Veterans' Affairs (DVA), the Persian Gulf Health Registry (PGHR), and in 1994 by the DoD, the Comprehensive Clinical Evaluation Program (CCEP). These programs were established to gather information from veterans regarding their wartime exposures and health histories and to offer veterans the opportunity to have comprehensive physical and laboratory examinations of their health. Veterans who choose to participate are clinically examined (including laboratory analysis of blood and urine samples) and administered a questionnaire regarding medical and family history, symptoms, recent debilitating illnesses, and self-perceived wartime exposures to specific risk factors (e.g., combat and specific chemicals) (Joseph et al., 1997; PGVCB, 1995).

Participation in these health registries is voluntary. The registries provide useful information to describe the health status of participants, but general prevalence rates of illnesses among Gulf War veterans cannot be assessed because participants are self-selected and do not constitute a representative sample of all U.S. soldiers who served in the Gulf region. Furthermore, no control group is available for comparison of rates of illness.

Table 1 cites the frequencies of diagnoses and the most frequent symptoms recorded for 20,000 participants in the CCEP registry through April 1, 1996 (DoD, 1996; Joseph et al., 1997). The diagnostic categories are based on the *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9) established by the U.S. Department of Health and Human Services (DHHS, 1998).

Table 1. Frequencies of symptoms and diagnoses for 20,000 Gulf War veterans participating in the DoD Comprehensive Clinical Evaluation Program (CCEP - through April 1, 1996). Adapted from DoD, 1996 (symptoms) and Joseph et al., 1997 (diagnoses).		
<b>Self-reported Symptoms</b> (13 most frequent symptoms: 10% of participants had no complaints)	<b>Chief Complaint</b> (%)	<b>Any Complaint</b> (%)
Joint pain	11	49
Fatigue	10	47
Headache	7	39
Memory loss	4	34
Sleep disturbance	2	32
Skin rash	7	31
Difficulty concentrating	<1	27
Depression	1	23
Muscle pain	1	21
Diarrhea	2	18
Dyspnea (shortness of breath)	3	18
Abdominal/gastrointestinal pain	3	17
Hair loss	<1	12
<b>Diagnostic Category</b>	<b>Primary Diagnosis</b>	<b>Secondary Diagnosis</b>
Disease of musculoskeletal system & connective tissue	18.6	29.5
Mental disorders	18.3	17.9
Symptoms, signs, ill-defined conditions	17.8	32.6
Respiratory system diseases	6.8	10.8
Skin and subcutaneous tissue diseases	6.3	13.7
Digestive system diseases	6.2	14.1
Nervous system & sense organ diseases	5.8	12.3
Infectious and parasitic diseases	2.6	6.4
Circulatory system diseases	2.2	5.9
Endocrine, nutritional & metabolic diseases & immunity disorders	2.1	6.1
Genitourinary diseases	1.3	4.2
Injury and poisoning	0.8	2.4
Neoplasms	0.8	2.1
Blood & blood-forming organ diseases	0.6	2.6
Congenital anomalies: conditions originating in perinatal period	0.2	0.9

Table 2 lists the ten most frequent self-reported symptoms and the distribution of diagnoses for 52,835 participants in the DVA PGHR, as of August 1997, showing similar frequencies of symptoms and diagnoses as those in the DoD CCEP (DVA, 1998a).

A more recent combined analysis of data in both the DoD and DVA registries through December 1997 (DVA, 1997 as cited in U.S. Senate, 1998) indicated that the frequencies of diagnoses were similar to the CCEP analysis by Joseph et al. (1997). Both registries indicate that there is concern among veterans regarding their health: 85,000 U.S. Gulf War veterans participated in the two clinical programs through 1997 (DVA, 1997 as cited in U.S. Senate, 1998).

Table 2. Frequencies of self-reported symptoms and diagnoses in 52,835 participants in the DVA Persian Gulf Health Registry (PGHR). Data as of August, 1997. Source: DVA, 1998a.		
Symptoms	Number	Percent
Fatigue	10,847	20.5
Skin rash	9,719	18.4
Headache	9,525	18.0
Muscle, joint pain	8,871	16.8
Loss of memory and other general symptoms	7,406	14.0
Shortness of breath	4,190	7.9
Sleep disturbances	3,111	5.9
Diarrhea and other gastrointestinal symptoms	2,416	4.6
Other symptoms involving skin and integumentary tissue	1,916	3.6
Chest pain	1,847	3.5
No complaint	6,496	12.3
Diagnostic Category	Number	Percent
No medical diagnosis	13,998	26.5
Musculoskeletal and connective tissue	13,299	25.2
Mental disorders	7,995	15.1
Respiratory system	7,540	14.3
Skin & subcutaneous tissue	7,144	13.5
Digestive system	6,028	11.4
Nervous system	4,398	8.3
Circulatory system	3,747	7.1
Infectious diseases	3,715	7.0
Injury and poisoning	2,485	4.7
Genitourinary system	1,774	3.4
Neoplasm	232	0.4

In 1993, the British Ministry of Defence established a clinical assessment program, the Medical Assessment Programme, for British Gulf War veterans that is similar to the DVA PGVHR and the DoD CCEP (Coker, 1996). Among the approximately 51,000 British troops who were deployed to the Gulf region, 1,026 registered in this program by June 1996, and 608 completed the program. Coker (1996) reported on an analysis of information for 284 of the veterans who completed the program. Although from a much smaller study population, the frequencies of

symptoms and diagnoses among the examined British Gulf War veterans (see Table 3) show some similarities to the results in Tables 1 and 2.

Table 3. Frequencies of Symptoms and Diagnoses for 284 participants in the British Ministry of Defence Medical Assessment Programme. Adapted from Coker, 1996.	
Symptom	Subjects reporting symptom (%)
Tiredness	55%
Muscle & joint pain	35%
Irritability	29%
Sleep disturbance	24%
Short-term memory loss	22%
Breathlessness	21%
Skin problems	16%
Tingling in limbs	11%
Principal Diagnostic Category (using ICD-9)	Frequency
Psychological conditions	35%
Signs, symptoms, and ill-defined conditions & chronic fatigue syndrome	15%
Respiratory system	9%
Skin and subcutaneous tissue	8%
Digestive system	7%
Nervous system	6%
Musculoskeletal system & connective tissue	6%
Circulatory system	3%
Genitourinary system	2%
Infectious diseases	1%
Endocrine	1%
Neoplasms	1%

The frequencies and types of symptoms and diagnoses of illnesses in participants in these clinical programs show that:

- C common health problems involve a wide variety of organ systems including the musculoskeletal, gastrointestinal, respiratory, and nervous systems;
- C a significant proportion of participants (20-30%) reported common symptoms (e.g., fatigue, headache, nervousness, heartburn, insomnia) that were without a clear physiologic or psychologic basis. Clinicians were not able to assign a standard diagnosis to these patients other than *symptoms, signs and ill-defined conditions*; and
- C three diagnostic categories (psychological conditions, musculoskeletal diseases, and symptoms, signs and ill-defined conditions) represented more than 50% of the primary diagnoses.

The most frequent symptoms reported as a chief complaint by the 3,558 DoD CCEP participants who were assigned to the diagnostic category, *symptoms, signs, ill-defined conditions*, were: fatigue (20%), headache (9.2%), memory problems (6.3%), sleep disturbances (4.7%), skin rash (4.4%), joint pain (4.2%), and shortness of breath (1.8%) (Joseph et al., 1997). Twenty-six percent (914/3558) of these participants reported multiple symptoms without designating a chief complaint.

Hyams et al. (1996) noted that symptom patterns for Gulf War veterans are consistent with the experiences of U.S. veterans of previous wars. Reviewing English-language articles and books of war-related illnesses associated with the Civil War, World Wars I and II, the Korean Conflict, and the Vietnam War, Hyams recognized two general categories of war-related illnesses that were diagnosed after each of these wars: 1) psychological illnesses<sup>2</sup>; and 2) physiological illnesses<sup>3</sup>. The physiological illnesses were primarily defined by self-reported, chronic (i.e., long-lasting) symptoms including fatigue, shortness of breath, headache, sleep disturbances, impaired concentration, and forgetfulness. Hyams noted that these symptoms are non-specific and are frequently found in all adult populations, as well as among persons with illnesses associated with psychological stress, and that, in each of these wars, the onset of these illnesses was preceded by a high frequency of diarrhea. Hyams concluded that “poorly understood war syndromes” have recurred since the U.S. Civil War, that no single disease or underlying cause that is unrelated to psychological stress is apparent from his review, and that the relationships between chronic, non-specific symptoms and physiological and psychological illness need to be better understood.

Because of the limitations of the information from the health registry programs<sup>4</sup>, the DVA is conducting a three-phase National Health Survey of Gulf War veterans to obtain estimates of nationally representative prevalences of symptoms and other medical conditions among all U.S. Gulf War veterans, (DVA research project # 2; RWG, 1998, 1999). Phase 1 involved mailing a questionnaire to 30,000 randomly selected U.S. veterans (15,000 Gulf War veterans and 15,000 veterans who served during the period of the Gulf War, but were not deployed to the Gulf region). Phase 2 interviewed, by telephone, a sample of 8,000 non-respondents, and validated (through records review) self-reported data for randomly selected respondents (2,000 deployed and 2,000 non-deployed). Phase 3 involves comprehensive clinical examination of the 4,000 respondents (and their families) selected in Phase 2. Analysis of collected data is not available to date.

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<sup>2</sup> Given various names through the years from *nostalgia* in the Civil War, through *shell shock* in WWI, and *battle fatigue* in WWII and Korea, to *post-traumatic stress disorder* after the Vietnam and Gulf Wars.

<sup>3</sup> *Da Costa syndrome* (irritable heart) after the Civil War, *Effort syndrome* during and after WWI and II, *Agent Orange exposure* after Vietnam, and *Gulf War syndrome*.

<sup>4</sup> For example, participants are not a random sample of all Gulf War veterans and there is no control group to compare prevalences.

## ***Conclusions and Research Recommendations from Review Panels***

Four panels of experts have evaluated available data from the DoD and DVA health registries and other sources of information regarding illnesses among Gulf War veterans: the *Defense Science Board Task Force on Persian Gulf War Health Effects* (DSB, 1994); the *National Institutes of Health Technology Assessment Workshop Panel* (NIH, 1994a,b); the *Institute of Medicine Committee to Review the Health Consequences of Service During the Persian Gulf War* (IOM, 1996b); and the *Presidential Advisory Committee on Gulf War Veterans' Illnesses* (PAC, 1996a,b; 1997). Appendix A of this document provides an historical account of the establishment of these and other panels reviewing various aspects of illnesses among Gulf War veterans and also summarizes panel recommendations. Each of the panels concluded that there was no evidence consistent with the existence of a unique disease among Gulf War veterans (DSB, 1994; NIH, 1994a,b; IOM, 1996b; PAC, 1996a,b, 1997).

The panels considered a number of suggested causes of illnesses among Gulf War veterans including combat- and deployment-related stress, chemical and biological warfare agents, vaccines, pesticides, pyridostigmine bromide, infectious diseases, depleted uranium, smoke from oil-well fires, petroleum products, and exposures to mixtures of chemicals specific to the Gulf War experience (see Appendix B: *Exposure to Chemicals During the Gulf War* for further discussion of potential Gulf War health risk factors). Given the broad range of illnesses noted among Gulf War veterans and the incomplete exposure data that were available, each of the panels concluded that no single cause of the multiple illnesses could be established (DSB, 1994; NIH, 1994a,b; IOM, 1996b; PAC, 1996a,b, 1997). The Presidential Advisory Committee on Gulf War Veterans' Illnesses made three further conclusions that: 1) it was unlikely that the reported illnesses were caused by exposure to any of the previously mentioned physical risk factors; 2) stress was likely to be an important contributing risk factor; and 3) research should be pursued in areas of uncertainty, such as the long-term effects of low-level exposure to chemical warfare agents and the synergistic effects of exposure to pyridostigmine bromide and other risk factors (PAC, 1996a,b, 1997; Lashof and Cassells, 1998).

The Presidential Advisory Committee further recommended that, "To ensure credibility and thoroughness, further investigation of possible chemical or biological warfare agent exposures during the Gulf War should be conducted by a group independent of DoD." (PAC, 1996b, 1997). In response to this recommendation, President Clinton created the Special Oversight Board for Department of Defense Investigations of Gulf War Chemical and Biological Incidents "to provide advice and recommendations based on review of DoD investigations into possible detections of, and exposures to, chemical or biological weapons agents and environmental and other factors that may have contributed to Gulf War Illnesses" (PSOB, 1998). This group held its first public hearing in November, 1998.

In response to another recommendation from the Presidential Advisory Committee (PAC, 1997), the DVA contracted the Institute of Medicine of the National Academy of Sciences to conduct a periodic review of scientific evidence regarding associations between illnesses and Gulf War

service. To carry out this review, the Institute of Medicine Committee on Health Effects Associated with Exposures During the Gulf War was formed in 1998 and held its first meeting in January 1999 (IOM, 1998a).

Initial research recommendations from the review panels included:

- C epidemiological research to compare prevalence rates of illnesses in Gulf War veterans with appropriate control populations;
- C research to examine groups of symptomatic Gulf War veterans more closely with neuropsychological and psychological tests; and
- C research on specific risk factors such as stress, pesticides, depleted uranium, and Leishmaniasis (DSB, 1994; NIH, 1994a,b; IOM, 1996b; PAC, 1996a).

More recent research recommendations include:

- C research into the long-term effects of low-level exposure to chemical warfare agents, alone and in combination with exposure to other Gulf War health risk factors including stress, pesticides and pyridostigmine bromide;
- C epidemiological research on groups of U.S. troops known to be in the vicinity of Khamisiyah when low-level exposure to nerve agents may have occurred;
- C research emphasis should include investigations of the causes, methods of prevention, and methods of treatment of musculoskeletal conditions and stress-related disorders (PAC, 1996b, 1997).

The Institute of Medicine established the Committee on Measuring Health Status of Persian Gulf Veterans in 1998 to identify important research questions regarding Gulf War illnesses and develop research designs and methods to address the questions (IOM, 1998b). The committee held a workshop in May 1998 (IOM, 1998c), but the committee's findings and recommendations are not yet available.

Overviews of research results and ongoing research on illnesses among Gulf War veterans are presented in sections 5 and 6 and Appendices C and D of this document.

#### **4. Overview: U.S. Government-Supported Research on Gulf War Illnesses**

In response to Public Law 102-585, President Clinton, in August, 1993, named the Secretary of Veterans Affairs to coordinate executive branch-funded research on the health consequences of the Gulf War. The Persian Gulf Veterans Coordinating Board (PGVCB) was formed in January, 1994 to coordinate interagency efforts in research, clinical care, disability compensation, resource allocation, and information dissemination. The Secretaries of the DoD, the DVA, and the DHHS chair the PGVCB. The RWG was established to assess the state and direction of research, identifying gaps in factual knowledge and conceptual understanding, identify testable hypotheses, recommend research directions for participating agencies, review research concepts as they are developed, and collect and disseminate scientifically peer-reviewed information (RWG, 1998).



In the 1994-1997 period, the RWG coordinated U.S.-government sponsorship of 121 research projects pertaining to illnesses in Gulf War veterans (RWG, 1998). New projects were funded in 1998.

As reported in the March 1998 RWG Annual Report to Congress, 39 of the 121 projects were completed through February, 1998. Total funding for research on Gulf War illnesses in the DoD, DVA, and the DHHS (in millions of dollars) was \$7.1 in 1994, \$17.3 in 1995, \$18.8 in 1996, \$34.2 in 1997, and \$37.9 (projected) in 1998 for a total of \$115 million to date (RWG, 1998).

In 1995 and 1996, the RWG established six focus areas of research:

- C Symptoms/General Health
- C Brain and Nervous System
- C Reproductive Health
- C Pyridostigmine Bromide
- C Environmental Toxicology
- C Leishmaniasis.

In response to the 1996 DoD announcement that U.S. troops demolished an Iraqi weapons bunker at Khamisiyah in March of 1991 and that certain troops may have experienced low-level exposure to nerve gas, the RWG (1998) added two additional focus areas related to possible health effects from low-level exposures to chemical weapons agents:

- C epidemiological research on health outcomes in troops potentially exposed to sarin at Khamisiyah; and
- C research on potential health effects from low-level, sub-clinical exposures to chemical warfare nerve agents, alone and in combination with exposure to other agents.

Ongoing, U.S. Government-funded research projects related to Gulf War illnesses and of interest to the focus of the current research-planning conference are briefly described in Appendix D and include:

- C seven projects related to multiple symptom illnesses such as *multiple chemical sensitivity* and chronic fatigue syndrome;
- C six projects (two human studies and four animal studies) related to *genetic differences in susceptibility to chemicals or stress*;
- C thirteen projects (all animal studies) related to *toxic effects from mixtures of chemicals and other risk factors* (e.g., effects of sarin, pyridostigmine bromide and DEET, alone or in combination, on neurobehavior and immune function in rats);
- C four projects related to *treatment of Gulf War symptoms* (two clinical trials of antibiotic treatment, one clinical trial examining cognitive behavioral therapy and aerobic exercise; and one animal study examining behaviorally-active drugs to modify behavior in mice);
- C eight projects (three epidemiological studies and five animal studies) related to *toxicity of low-level, subclinical exposures to chemical warfare agents* (all but one project is related to exposure to nerve agents; the other examines possible DNA effects from nitrogen mustard);

- C six projects (one human controlled-exposure study and five animal studies) related to *toxicity of pyridostigmine bromide*;
- C and numerous clinical and epidemiological studies related to *assessment and definition of Gulf War illnesses* and quantification of *disease prevalence and associations between chemical exposures and disease*.

## 5. Gulf War Illnesses: Research Results and Ongoing Research

This section discusses results from research related to illnesses in Gulf War veterans and relationships of the results to ongoing research projects. Included in the discussion are results from mortality and hospitalization studies, studies of self-reported symptoms in Gulf War-deployed and non-deployed veterans, studies of neurophysiological and neuropsychological variables in symptomatic Gulf War veterans, studies of health effects from mixtures of chemicals used in the Gulf War and other risk factors, studies of genetic differences in susceptibility to environmental agents, studies of multiple chemical sensitivity in Gulf War veterans, and studies of treatment of Gulf War veterans with non-specific chronic symptoms of ill health. Appendix C: *Research on Gulf War Illnesses: Description and Evaluation of Selected Studies* and Appendix D: *Ongoing Research Related to Illnesses Among Gulf War Veterans* provide additional details.

### *Mortality and Hospitalization Studies*

Large-scale studies are available comparing the following in active-duty U.S. military personnel who served in the Gulf War with active-duty personnel who did not serve in the Gulf :

- C rates of mortality (Writer et al., 1996; Kang and Bullman, 1996, 1997);
- C rates of general hospitalizations (Gray et al., 1996);
- C rates of hospitalizations for unexplained illnesses (Knoke and Gray, 1998);
- C rates of hospitalization for testicular cancer (Knoke et al., 1998); and
- C rates of general birth defects and a specific birth defect, Goldenhar syndrome (Cowan et al., 1997; Aranata et al., 1997).

The mortality rate studies found no differences between Gulf War-deployed and non-deployed personnel, except for a higher rate of mortality from unintentional injuries (i.e., accidents, in particular motor vehicle accidents) in deployed personnel (Writer et al., 1996; Kang and Bullman, 1996, 1997). The hospitalization studies, which focused on discharge rates from U.S. military hospitals, found no consistent evidence for increased hospitalizations in Gulf War-deployed personnel (Gray et al., 1996; Knoke and Gray, 1998; Knoke et al., 1998). The studies of children of deployed-personnel born in U.S. military hospitals found no statistically significant increase in

general birth defects or in Goldenhar syndrome<sup>5</sup> compared with children born to non-deployed personnel (Cowan et al., 1997; Aranata et al., 1997).<sup>6</sup>

Whereas these large-scale studies have not found evidence for increased incidence of grave illness among Gulf War veterans, they have several limitations including: not studying personnel who separated from the military; not studying geographically or exposure-defined subgroups; not examining non-military hospitalizations; and not examining outpatient treatment of illness (see Appendix C for more discussion). These studies, thus, do not negate the fact that Gulf War veterans have experienced, and still are experiencing, real illnesses, as demonstrated by the DVA and DoD clinical experiences. Discussion of the strengths and limitations of the published mortality, hospitalization, and reproductive-outcome studies are available in the literature (Doyle et al., 1997; Haley, 1998a,b; Kang and Bullman, 1998; Gray et al., 1998; Cowan et al., 1998). With respect to the possibility that reproductive outcomes (e.g., increased risk for fetal deaths, birth defects, miscarriages, medical termination of pregnancy, and infertility) might be influenced by Gulf War service, there are several on-going controlled epidemiological studies that were designed with these limitations in mind, but for which data are not yet available (see Doyle et al., 1997; RWG, 1997, 1998, 1999; Cowan et al., 1998).

### *Studies of Self-reported Symptoms in Gulf War-Deployed and Non-deployed Veterans*

Results from several studies are available comparing self-reported health symptoms and medical conditions in groups of Gulf War deployed and non-deployed veterans (CDC, 1995; Fukuda et al., 1998; Iowa Persian Gulf Study Group, 1997; Stretch et al., 1995; Pierce, 1997; Canadian Department of National Defence, 1998; Unwin et al., 1999; Ismail et al., 1999; Proctor et al., 1998 ). These studies have found consistently higher rates of self-reported symptoms in deployed compared with non-deployed veterans; short descriptions of results follow. Results from these studies should be evaluated with the generally accepted understanding that self-reported symptoms are subject to individual and group biases (“recall biases”) that can distort the magnitude of differences between groups. (More study details are included in Appendix C)

The CDC (1995) compared rates of self-reported health symptoms that persisted for more than six months among Gulf War deployed and non-deployed, active-duty personnel in Air Force units

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<sup>5</sup> Goldenhar syndrome is a prenatal developmental disorder that leads to abnormal ear and facial structures; anecdotal reports in the popular press in 1995 suggested that there might be an excess of this birth defect among children of Gulf War veterans (Aranata et al., 1997).

<sup>6</sup> In addition to these studies of active-duty personnel, early news-media reports that there was an apparent cluster of birth defects in Gulf-deployed Mississippi National Guard units were not supported by a subsequent examination of the frequencies of birth defects, low-birth weight, or premature births in 54 of 55 children born to 52 veterans in these units compared to U.S. national rates, but the small sample size in this study does not allow a definitive conclusion that applies to all Gulf War veterans (Penman et al., 1996).

from Pennsylvania and Florida and found that the prevalence of each of thirteen symptoms<sup>7</sup> was significantly greater in deployed personnel compared with non-deployed personnel. Individuals in a sample of this study population were defined either as “cases” with chronic multiple symptoms or “noncases” based on their survey responses<sup>8</sup> and evaluated further in physical examinations, laboratory tests of blood, stool and urine samples, and serological examinations (Fukuda et al., 1998). Fukuda et al. (1998) reported that: 1) “cases” with chronic multiple symptoms were more frequent in the deployed group compared with the non-deployed group; 2) no findings in the physical, laboratory or serological tests were predictive of case definition<sup>9</sup>; and 3) no significant associations were found between having chronic multiple symptoms and several surrogate measures of exposure (e.g., date of deployment, season of deployment, occupational activity during war).

The Iowa Persian Gulf Study Group (1997) found significantly higher prevalence of similar self-reported symptoms indicative of several syndromes or disorders<sup>10</sup> in a group of Gulf War-deployed personnel from Iowa who served in U.S. regular military, National Guard, or reserve units compared with a similar group of non-deployed military personnel from Iowa. Stretch et al. (1995; 1996a,b) also found significantly higher percentages of self-reported physical health symptoms in Gulf-deployed veterans from Hawaii and Pennsylvania compared with non-deployed veterans, and noted that this difference was not explained by several demographic variables (e.g., age, rank, marital status) other than deployment.

In a study of female U.S. veterans, Pierce (1997) reported that self-reported frequencies of occurrence of general health symptoms<sup>11</sup> were higher in deployed versus non-deployed veterans, but the differences were not statistically significant. However, self-reported frequencies of occurrence of other symptoms<sup>12</sup> (lumps or cysts in breasts, abnormal Pap smear, headache) were statistically significantly higher, four years after the war, in deployed veterans than in non-deployed veterans, and a significantly greater percentage of deployed veterans (24%) met the

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<sup>7</sup> For example: fatigue, joint pain, nasal congestion, diarrhea, joint stiffness, unrefreshing sleep.

<sup>8</sup> A case was defined as reporting one or more chronic symptom from at least two of three categories: fatigue, mood-cognition and musculoskeletal.

<sup>9</sup> Fukuda et al. (1998) reported that “mean values of a few routine blood tests differed among cases and noncases, but the differences were marginal and clinically unimportant”. They noted that a more detailed summary of blood and urine data was available by request.

<sup>10</sup> For example: depression, posttraumatic stress disorder, chronic fatigue, cognitive dysfunction, asthma, and fibromyalgia.

<sup>11</sup> Rash, cough, depression, unintentional weight loss, insomnia and memory problems.

<sup>12</sup> Pierce (1997) termed these symptoms *gender specific*.

requirement for combat-related posttraumatic stress disorder (PTSD) than non-deployed veterans (15%) (Pierce, 1997).

In a study of self-reported health symptoms in Canadian Gulf War veterans compared with non-Gulf-deployed Canadian veterans, Gulf-deployed veterans reported higher prevalences of symptoms of chronic fatigue, cognitive dysfunction, multiple chemical sensitivity, major depression, post-traumatic stress disorder, anxiety, fibromyalgia and respiratory diseases (bronchitis and asthma together), as well as higher numbers of children with birth defects (before, during, and after the Gulf War) (Canadian Department of National Defence, 1998).

Investigators at the Boston Environmental Hazards Center found significantly higher percentages of veterans who reported health symptoms<sup>13</sup> in Gulf-deployed groups from New England (n= 186) and New Orleans (n = 66) compared with a group of U.S. veterans (n = 48) who were deployed to Germany during the Gulf War period (Proctor et al., 1998). Statistical analysis of symptom scores (that were based on self-reported frequency of occurrence of the symptoms) and self-reported military-experience exposures found significant associations between specific symptoms<sup>14</sup> and exposures to pesticides, debris from Scud missiles, chemical or biological warfare agents, and smoke from tent heaters.

In a survey study of U.K. veterans, significantly higher percentages of Gulf-deployed veterans reported numerous health symptoms<sup>15</sup> compared with non-deployed veterans from the same era or veterans deployed to Bosnia (Unwin et al., 1999). Most of these differences persisted after statistical adjustment for possible confounders and diagnosed psychological disorders. Statistical associations between self-reported symptoms and self-reported exposures to numerous health risk factors<sup>16</sup> were examined in each of the studied groups, after defining individuals with multiple

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<sup>13</sup> Skin rashes, stomach cramps or excessive gas, joint pains, headaches, difficulties learning new material, inability to fall asleep, and frequent periods of anxiety or nervousness.

<sup>14</sup> The analysis excluded 12 subjects in the Gulf-deployed groups who were diagnosed with current PTSD. Statistically significant associations included those between: 1) self-reported exposure to pesticides and musculoskeletal or neurological symptoms; 2) self-reported exposure to debris from Scud missiles and musculoskeletal, neurological, neuropsychological or psychological symptoms; 3) self-reported exposure to chemical or biological warfare agents and musculoskeletal, neurological, neuropsychological, and psychological symptoms; and 4) self-reported exposure to smoke from tent heaters and cardiac, neurological, and pulmonary symptoms.

<sup>15</sup> For example, fatigue, sleep disturbances, irritability, headaches, loss of concentration, joint stiffness or pain, tingling in fingers and arms, chest pain, and night sweats

<sup>16</sup> For example, smoke from oil-well fires, use of personal pesticides, use of pyridostigmine bromide, belief of exposure to chemical attack, multiple routine vaccinations, or vaccinations for biological warfare agents.

symptoms<sup>17</sup> as “cases” and others as “noncases”. In all three groups of veterans, statistically significant associations were found between reporting multiple symptoms and reporting exposure to numerous agents, including nerve gas, exhaust from heaters or generators, and pyridostigmine bromide. A weak, although statistically significant, association between reporting multiple symptoms and reporting receiving multiple vaccinations was found in the Gulf-deployed U.K. veterans, but not in the Bosnia U.K. veterans (Unwin et al., 1999). In a companion study, Ismail et al. (1999) used a mathematical technique, two-step factor analysis, to examine if the self-reported symptoms represented a unique Gulf War disorder. Using this technique, a three-factor structure was identified among the Gulf-deployed veterans; the “factors” were labeled mood, respiratory system and peripheral nervous system based on their defining symptoms. Ismail et al. (1999) reported that this three-factor structure also reasonably fit the Bosnia-deployed veterans and the non-deployed, Gulf War-era veterans, and concluded that their findings do not support a unique Gulf War syndrome.

Other studies also looked for relationships between self-reported health symptoms and measures of stress or self-reported exposures to specific health risks such as combat, poisonous gas or occupational exposure to petroleum products (Stretch et al., 1996a,b; Baker et al., 1997; Wolfe et al., 1998). Relationships between war-related stress and physical symptoms of ill-health were found (Stretch et al., 1996a,b; Baker et al., 1997), but these studies do not indicate the strength of the relationship and do not exclude possible relationships between symptoms and other risk factors. One study found that, in a group of Gulf-deployed U.S. veterans, self-reported exposure to poisonous gas was related to higher symptom reporting (Wolfe et al., 1998).

Based on the results of several psychological tests, Stretch et al. (1996a,b) reported that, in addition to more frequently reporting health symptoms, deployed veterans from Hawaii and Pennsylvania exhibited more stress than non-deployed veterans. In a study of 188 Gulf War veterans, half of whom were patients at the Cincinnati Veterans’ Administration Medical Center, Baker et al. (1997) found that the 24 Gulf War veterans in this group with PTSD had statistically significantly greater combat exposure and reported more symptoms than others in the group. Wolfe et al. (1998) found that, in a study of 2,119 Gulf-deployed troops who returned to the U.S. through Fort Devens, veterans who reported having been exposed to poison gas were more likely to report health symptoms (such as aches/pains, lack of energy, etc.), even after excluding from the analysis those subjects with presumptive PTSD, and that deployed veterans with combat exposure or occupational exposure to motor vehicles (i.e., petroleum products) were not more likely to report health symptoms.

As discussed earlier, an on-going large-scale project, the VA National Health Survey, is designed to estimate and compare the prevalence of various symptoms, medical conditions, and unexplained illnesses in Gulf War-deployed and non-deployed U.S. veterans and look for relationships between exposure to specific risk factors and frequencies of health symptoms (DVA

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<sup>17</sup> Following the convention of Fukuda et al. (1998), a case was defined as reporting one or more chronic symptom from at least two of three categories: fatigue, mood-cognition and musculoskeletal.

research project #2; RWG, 1998, 1999). Data from this project are not currently available. Other on-going large-scale projects for which data are not yet available include:

- C a University of Oregon study comparing health survey responses and clinically evaluated neuropsychological and neurophysiological variables in: subjects from U.S. troops located within a 50-km radius of Khamisiyah in March, 1991; subjects from other U.S. Desert Storm and Desert Shield troops; subjects from other U.S. troops that were not deployed to the Gulf region; and civilians with a documented history of exposure to organophosphate insecticides (DoD research project #63; RWG, 1998, 1999); and
- C an Institute of Medicine/Medical Follow-up Agency study comparing hospitalization rates and mortality rates during a 5-year post-Gulf War period in: subjects directly involved in the March 1991 Khamisiyah demolition, subjects from two battalions located within a 50-km radius of the Khamisiyah demolition site during March, 1991; subjects from Gulf War battalions never located within a 50-km radius of Khamisiyah; and subjects from non-deployed U.S. troops (DoD research project #69; RWG, 1998, 1999).

### ***Neurophysiological and Neuropsychological Evaluations of Symptomatic Gulf War Veterans***

Several studies have carried out neurophysiological and neuropsychological evaluations of small groups of symptomatic Gulf War veterans (Jamal et al., 1996; Amato et al., 1997; Goldstein et al., 1996; Axelrod and Milner, 1997; Haley et al., 1997a,b; Haley and Kurt, 1997). In general, these studies have not found obvious and consistent changes in objective measures of numerous neurophysiological or neuropsychological variables; however, some of the studies have found subtle changes in several variables in some of the examined patients. Several hypotheses concerning the cause or physiological basis of difficult-to-diagnose chronic illnesses among some Gulf War veterans remain plausible; some investigators hypothesize relationships to stress (e.g., Goldstein et al., 1996; Amato et al. 1997), whereas other investigators hypothesize relationships to low-level chemical exposure (Haley and Kurt, 1997).

In an evaluation of neuromuscular function<sup>18</sup>, Jamal et al. (1996) found statistically significant changes in two variables of nerve conduction velocity<sup>19</sup> and one variable of cold sensation in fourteen symptomatic<sup>20</sup> British Gulf War veterans compared with ten healthy civilians, but noted that the clinical relevance of these findings was unknown.

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<sup>18</sup> The evaluation included a physical examination of reflexes, muscle power, and response to stimulation (e.g., pin prick), nerve conduction velocity tests, electromyographic analysis of muscles, and quantitation of sensory thresholds to heat and vibration. 14 subjects (12 men and 2 women) were randomly selected by Jamal et al. from a list, compiled by a voluntary organization, of 40 U.K. veterans who complained of unexplained illness after the Gulf War.

<sup>19</sup> Among 19 nerve conduction and electrophysiological variables that were measured.

<sup>20</sup> These veterans reported musculoskeletal symptoms including fatigue, weakness, numbness and spontaneous sensations of heat or cold.

In evaluations of neuromuscular function and muscular structure<sup>21</sup> in 20 Gulf War veterans who complained of severe and debilitating muscle fatigue, weakness, or pain, Amato et al. (1997) reported that the only abnormalities<sup>22</sup> found were “mildly increased” levels of serum creatinine kinase or non-specific histological changes in biopsied muscle tissue in 8/20 of the patients. Amato et al. (1997) did not believe these changes to be clinically significant or indicative of a specific neuromuscular disorder.

Axelrod and Milner (1997) administered 36 neuropsychological tests to a group of 44 self-selected U.S. Gulf War veterans<sup>23</sup> and found that average performances for the group only showed slight, but statistically significant, impairments, relative to normal values, in two of six tests of finger dexterity and in three of twelve tests of executive functioning<sup>24</sup>.

Goldstein et al. (1996) compared performance by 21 symptomatic Gulf War veterans and 38 healthy civilian volunteers in a battery of neuropsychological tests<sup>25</sup>, and reported that no statistically significant differences were found between the two groups on scores in fourteen tests of cognitive processes (i.e., attention and memory). No statistically significant difference was found between the Gulf War veterans and the control group in a cognitive impairment index<sup>26</sup>, when adjustment for psychological distress was made (Goldstein et al., 1996).

Using a mathematical technique, principal factor analysis, to identify associations among symptoms reported by a group of 249 Gulf War veterans, Haley et al. (1997a) identified and named six possible syndromes and studied subjects with the three syndromes showing the strongest associations among symptoms: *impaired cognition* (associated with: attention,

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<sup>21</sup> The evaluation included physical examination, determinations of serum creatine kinase and erythrocyte sedimentation rate, thyroid function tests, nerve conduction velocity tests, repetitive nerve stimulation tests, electromyographical analysis of several muscle groups, and microscopic examination of biopsied muscle tissue.

<sup>22</sup> Amato et al. (1997) noted that the frequencies of abnormalities which they observed in their group of 20 patients were less than that seen in other larger studies in which patients were referred for in-depth evaluation of muscle pain.

<sup>23</sup> This group of veterans reported experiencing joint pain (65%), skin rashes (57%), fatigue (57%), sleep disturbances (50%), shortness of breath (41%), and cognitive difficulties (39%).

<sup>24</sup> The three executive function tests with lower scores involved color naming and word naming. The other executive functioning tests administered included Trail Making tests, card-sorting tests, oral word association tests, and a test of semantic fluency.

<sup>25</sup> Included were tests of attention, memory, psychomotor function, and problem solving.

<sup>26</sup> The impairment index was based on the number of tests performed by a subject in which the score was below one standard deviation of the mean of the control group.



memory, and reasoning problems; insomnia; depression; daytime sleepiness; and headaches), *confusion-ataxia* (associated with: thinking problems; disorientation; balance disturbances; vertigo; and impotence), and *arthro-myo-neuropathy* (associated with: joint and muscle pain; muscle fatigue; difficulty lifting; and extremity paresthesias). In 23 symptomatic “cases” with these syndromes and 20 controls<sup>27</sup>, Haley (1997b) examined performance in a battery of neuropsychological tests, auditory and vestibular function variables, brain stem auditory evoked potentials, somatosensory and visual evoked potentials, clinical motor and reflex functions, brain images, and numerous blood cytological and biochemical variables (see Appendix C for more details on administered tests and results). The following statistically significant differences between cases and controls were found: 6/22 cases showed weakness of the lower extremities compared with 1/20 controls; mean scores on composite indices of neuropsychological dysfunction were higher in cases than controls; and 4/23 cases versus 0/20 controls showed abnormal spontaneous nystagmus (rhythmic movement of the eyeball). In addition, mean values of several auditory and vestibular function variables<sup>28</sup> and several variables associated with evoked potentials<sup>29</sup> were significantly different (in the direction of impairment) in cases compared with controls.

The clinical significance of these differences is uncertain. Six neurologists, who were blinded to the identity of the subjects, reviewed the findings on each individual and concluded that “the clinical and laboratory findings were nonspecific and not sufficient to diagnose any known syndrome in any subgroup of the subjects.” Haley et al. (1997b) speculated that the observed statistically significant differences between cases and controls in several objective measures of neurophysiological and audiovestibular variables may have a relationship with “sublethal exposures to cholinesterase-inhibiting chemicals”, and noted that additional research is necessary, including examining the same, and additional, endpoints (e.g., neuromuscular and nerve conduction velocity variables) in a greater number of subjects (cases and controls).

Haley and Kurt (1997) hypothesized that the three previously discussed factor analysis-derived syndromes may represent variants of organophosphate-induced delayed peripheral neuropathy due to exposure to mixtures of anti-cholinesterase agents (e.g., chemical warfare nerve agents, pesticides, insect repellent, and/or pyridostigmine bromide). In support of this hypothesis, several statistically significant associations were found between self-reported exposures to anti-cholinesterase agents and the syndromes (e.g., wearing of pet flea and tick collars and *impaired cognition*; adverse reactions to pyridostigmine bromide and *confusion-ataxia* or *arthro-myo-*

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<sup>27</sup> Cases included 5 subjects with *impaired cognition*, 5 with *arthro-myo-neuropathy*, and 13 with *confusion-ataxia*. Controls, matched for age, sex, and educational level, included 10 deployed asymptomatic veterans and 10 non-deployed veterans. See Appendix C for more details.

<sup>28</sup> For example, increased interocular asymmetry in response to rotation.

<sup>29</sup> For example, increased latency of the lumbar-to-cerebral peaks on the posterior tibial somatosensory evoked potential.

*neuropathy*. See Appendix C for more details.) Landrigan (1997) has noted that the hypothesis put forth by Haley and colleagues is important and deserves serious investigation, but limitations<sup>30</sup> in the studies conducted to date “substantially weaken the authors’ strong conclusions.”

Several ongoing research projects are making efforts to identify specific physical or laboratory neurological variables that may be consistently affected in Gulf War veterans who are experiencing multiple chronic symptoms such as fatigue, headaches, and difficulty concentrating.

- C At the University of Texas Southwestern Medical Center (DoD research project #65; RWG, 1998, 1999), a battery of clinical and laboratory tests are being developed to assess neurological variables that may be differentially affected in subjects with unexplained, multiple chronic symptoms compared with healthy subjects (e.g., regional cerebral blood flow before and after challenge with a carbamate cholinesterase inhibitor, nerve firing rate of peroneal nerve, quantitative electroencephalographic pattern analysis, and blood levels of serum butyrylcholinesterase). This group is also developing a plan to conduct another health and exposure survey of randomly selected national samples of deployed and non-deployed Gulf War-era veterans.
- C At Georgetown University (DoD research project #31; RWG, 1998, 1999), several physiological variables (pain threshold, esophageal smooth muscle motility) and biochemical variables (changes in neurohormonal levels in response to different stressors, cerebral spinal fluid levels of neurotransmitters) are being examined in groups of ill Gulf-deployed veterans compared with groups of civilians experiencing similar multiple chronic symptoms and groups of healthy subjects.
- C At Boston University, brain activation patterns (determined with magnetic resonance imaging) will be examined in groups of ill and healthy Gulf War-deployed U.S. veterans, a group of Germany-deployed veterans of the Gulf War era, and a group of ill, non-Gulf War deployed veterans (DHHS research project #5; RWG, 1999). Brain activation patterns will be assessed in subjects challenged with a test of working memory, a brain function thought to be affected in various disorders such as chronic fatigue syndrome, multiple chemical sensitivity, and post-traumatic stress disorder. This project will also administer neuropsychological tests to two groups of Danish veterans. One group was deployed to the Persian Gulf region in 1991 after the ground war ceased, and the other was not deployed to the Gulf.

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<sup>30</sup> Landrigan (1997) noted that the studies are focused on a single battalion of naval construction workers whose Gulf War experiences may not be representative of most Gulf War veterans; that only 41% of the battalion participated in the examinations raising the possibility of selection bias; that most information collected on illnesses was self-reported - detailed clinical and neuropsychological examinations were performed on only 23 symptomatic veterans representing less than 4% of the battalion; that motor nerve conduction velocity tests to confirm organophosphate-induced delayed peripheral neuropathy were made on only 5 veterans; and that exposure information was entirely self-reported.

### *Studies of Neurological Effects from Mixtures of Chemicals and other Risk Factors*

As discussed in the previous section, there is limited suggestive evidence for the hypothesis that some Gulf War veterans with chronic, non-specific symptoms may be experiencing neurological dysfunction due to low-level exposures to mixtures of anti-cholinesterase agents that might have additive or synergistic effects (Haley et al., 1997a,b; Haley and Kurt, 1997).

Suggestive evidence of additive or synergistic effects among anti-cholinesterase agents is provided by three animal studies of acute (i.e., short-term) exposure: one with hens exposed to the anti-nerve agent, pyridostigmine bromide, the insect repellent, DEET, and the insecticide, permethrin, alone and in various combinations with each other (Abou-Donia et al., 1996a)<sup>31</sup>; another with hens exposed to pyridostigmine bromide, DEET, and the insecticide, chlorpyrifos, alone and in combination<sup>32</sup> (Abou-Donia et al., 1996b); and a third with rats given single doses of pyridostigmine bromide, DEET, and permethrin, alone and in various combinations<sup>33</sup> (McCain et al., 1997). The rat study found a significant increase in lethality when all three compounds were given compared with expected additive values based on lethality from exposure to the individual compounds; these findings suggest that the compounds interacted in a synergistic (greater than additive) manner (McCain et al., 1997). In the hen studies, individual compounds were administered at exposure levels that produced mild signs of neurological effects (e.g., transient leg weakness or diarrhea) and no, or minimal, microscopic changes in spinal cords or sciatic nerves (Abou-Donia et al., 1996a,b). Co-exposure to various combinations of two of the compounds produced signs of greater neurotoxicity (e.g., gait disturbances, tremors) and mild to moderate microscopic changes in the spinal cord and sciatic nerve of some of the hens; co-exposure to all three compounds produced marked neurotoxic signs and mild to severe changes in spinal cords and sciatic nerves (Abou-Donia et al., 1996a,b). Although the design of the hen studies does not allow definitive conclusions about synergistic interactions, the results suggest that additive effects occurred. The physiological or biochemical basis of these interactions is not

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<sup>31</sup> Hens were exposed 5 days/week for 2 months to oral doses of 5 mg/kg-day pyridostigmine bromide, subcutaneous doses of 500 mg/kg-day DEET, and subcutaneous doses of 50 mg/kg-day permethrin, alone, in binary combination, or all three together. Although the individual doses of these compounds did not produce marked neurotoxic effects in the hens, they were higher than doses experienced by Gulf War soldiers; for example, the prescribed dose of pyridostigmine bromide of 30 mg per 8 hours corresponds to about 1.3 mg/kg-day for a 70-kg subject.

<sup>32</sup> Hens were exposed 5 days/week for 2 months to oral doses of 5 mg/kg-day pyridostigmine bromide, subcutaneous doses of 500 mg/kg-day DEET, and subcutaneous doses of 10 mg/kg-day chlorpyrifos, alone, in binary combination, or all three together.

<sup>33</sup> Rats were exposed to several oral doses of each compound alone to determine acute oral lethal dose-response relationships. Interaction studies were then conducted examining lethality that occurred when low-level exposure to two of the compounds was constant and the dosages of the third compound were varied.

understood, but Abou-Donia et al. (1996a,b) hypothesized that competition among the compounds for esterases in the liver and plasma may lead to impaired breakdown and subsequent increased concentrations in nervous tissues<sup>34</sup>.

The relevance of these animal studies to possible chronic neurological impairment in Gulf War veterans is uncertain due to the high exposure levels to which the animals were exposed<sup>35</sup>, differences in routes of administration, potential physiological differences between humans and the studied animals, and other potential differences between mixtures to which the animals were exposed and mixtures that may have been experienced by Gulf War veterans (e.g., use of insecticides and insect repellents may have been low in the winter of 1991 when the use of pyridostigmine bromide occurred).

Acute exposure to some cholinesterase-inhibiting agents, such as certain organophosphate and carbamate insecticides, at exposure levels that produce acute symptoms of poisoning<sup>36</sup> is documented to produce different types of delayed or chronic neurological effects including persistent performance deficits on neuropsychological tests (Rosenstock et al., 1991; Ecobichon, 1994a,b; Steenland et al., 1994). Recent studies of subjects who experienced acute sarin poisoning in the Tokyo, Japan subway incident provide additional evidence that persistent subtle neurological deficits or changes may occur following acute high-level poisoning from cholinesterase-inhibiting chemicals (Murata et al., 1997; Yokoyama et al., 1998a,b). However, there are fewer data concerning persistent or long-term neurological effects from acute low-level exposures to cholinesterase inhibiting agents. Mice exposed to air concentrations of the organophosphate nerve agent, sarin, that did not produce obvious acute signs or symptoms of neurological damage<sup>37</sup> developed signs of peripheral neuropathy after exposure ceased, suggesting that obvious acute symptoms may not be a requirement for later developing neurological effects (Husain et al., 1993). Another study measured impairment in spatial learning in rats throughout a 21-day period following a 14-day treatment period with a potent organophosphate cholinesterase inhibitor at a dose that did not produce obvious signs of neurotoxicity (Prendergast et al., 1997).<sup>38</sup>

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<sup>34</sup> Buchholz et al. (1997) reported that co-exposure of rats to pyridostigmine bromide and permethrin caused a 30% decrease in nervous tissue doses of permethrin compared with permethrin exposure alone, and concluded that their results do not support Abou-Donia's proposed mechanism.

<sup>35</sup> McCain et al. (1997) noted that to achieve the lowest doses used in the rat study, a person weighing 70 kg would have to simultaneously ingest 107 30-mg pyridostigmine bromide tablets, 23 six-ounce aerosol cans of 0.5% permethrin, and 6.6 two-ounce tubes of 33% DEET.

<sup>36</sup> Acute symptoms can include increased secretions, tremors, and mental confusion due to stimulation of cholinergic nerves in the central and peripheral nervous system.

<sup>37</sup> 5 mg/m<sup>3</sup>, 20 minutes/day for 10 days.

<sup>38</sup> Rats were given subcutaneous injections of 0, 50, 250, or 500 µg diisopropylfluorophosphate/kg per day for 14 days (Prendergast et al., 1997). Diisopropylfluorophosphate is a potent organophosphate

In contrast, a recent study found no symptoms of neurological effects in a group of rescue workers, one year after they were involved in a sarin incident in Matsumoto, Japan without experiencing acute symptoms of neurological effects (Nakajima et al., 1997).

Animal studies have indicated that physically-induced stress may disrupt the blood-brain barrier (Sharma et al., 1991; Friedman et al., 1996), thus leading to the hypothesis that war-related stress may have facilitated increased nervous system concentrations of pyridostigmine bromide and caused adverse acute neurological reactions that would not have occurred under non-stress conditions. In support of this hypothesis, Friedman et al. (1996) reported that, after mice were subjected to a stress-inducing forced-swim protocol, the dose of pyridostigmine bromide that was required to inhibit brain acetyl cholinesterase activity by 50% was reduced to less than 0.01 of the usual dose under non-stress conditions. Friedman et al. (1996) suggested that this hypothesis may partially explain the findings that acute symptoms of central nervous system dysfunction<sup>39</sup> were reported by more than 23% of 213 soldiers who took pyridostigmine under wartime conditions and were surveyed within 24 hours, whereas in a double-blind, placebo-controlled study under non-stressed conditions, about 8% of subjects given the same dose of pyridostigmine bromide reported similar acute symptoms. Whether or not stress-induced acute effects on the blood-brain barrier are related to subtle neurological changes observed in some Gulf War veterans with chronic non-specific symptoms of ill health remains unknown.

Numerous animal studies relevant to interactions between various neurotoxic Gulf War chemicals and other risk factors (such as stress and botulinum toxoid vaccination) are in progress or are being prepared for publication.<sup>40</sup> Given the extensiveness of this research effort, it appears that

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inhibitor of acetylcholine esterase. The highest dose produced obvious signs of neurotoxicity (slowed movement, ataxia) that were not observed at the lower doses; at the two lower doses, subtle changes in behavior were noted during treatment. In rats from the two lower dose groups, cognitive function was assessed in a test of spatial learning at several intervals up to 21 days after treatment ceased; performance was impaired in rats treated with 250 µg/kg, but not in 50-µg/kg rats.

<sup>39</sup> Headaches, insomnia, drowsiness, nervousness, difficulties in focusing attention.

<sup>40</sup> These projects include: an examination of neurobehavioral variables in rats exposed to jet fuel vapor alone and in various combinations with insect repellent (DEET), pyridostigmine bromide, and periodic electric shock to induce stress (DoD research project #2; RWG, 1999); evaluation of neurobehavior and immune function variables in rats exposed to pyridostigmine bromide, permethrin, and DEET, alone or in combination (DoD research project #37; RWG, 1999); examination of possible delayed neurobehavioral and neuropathological effects in rats or monkeys following exposure to various cholinesterase inhibiting chemicals, alone or in various combinations or in combination with the administration of botulinum toxoid (DoD research projects # 54 and 61; RWG, 1999); examination of possible delayed respiratory and nervous system effects in guinea pigs and marmosets exposed to low-levels of sarin, with or without pretreatment with pyridostigmine (DoD research project #55; RWG, 1999); examination of possible delayed effects on neuromuscular and sensory systems in mice and hens exposed to low levels of sarin alone or in combination with pyridostigmine bromide (DoD research project #56; RWG,

additional animal studies currently are not needed, at least until research results from the ongoing studies can be evaluated.

### *Genetic Differences in Susceptibility to Environmental Agents*

The Gulf War experience with and the clinical trials of the use of pyridostigmine bromide at the recommended dosage rate of 30 mg per 8 hours indicate that variable percentages of individuals experience acute symptoms of acetylcholinesterase inhibition including eye pain and headache, dizziness, runny nose, tightness in the chest, nausea, and/or abdominal cramps (Taylor, 1996; Keeler et al., 1991; Friedman et al., 1996). Keeler et al. (1991) reported that, during wartime use at this dose, the incidence of such “side effects” was around 1% and that about 0.1% of subjects experienced sufficiently severe effects to discontinue its use. Friedman et al. (1996) reported that in double-blind clinical trials with 35 healthy volunteers about 8% experienced acute symptoms of central nervous system dysfunction (e.g., headaches, insomnia, drowsiness, nervousness) and that, in studies with 213 soldiers under war-time conditions, similar symptoms were reported by about 24% of the subjects. In another report of the same study of 213 soldiers, Sharabi et al. (1991) noted that most individuals who experienced symptoms reported them as mild, but small percentages (3-10%) of subjects reported symptoms to be severe.

The underlying physiological, biochemical and/or genetic basis of why some individuals experience “side effects” from this pyridostigmine dosage rate is not understood and could vary from individual to individual. One hypothesis that is receiving some research attention is that differences among individuals in the level or the genotype of the blood serum enzyme, butyrylcholinesterase, may be responsible, at least in part, for differences among individuals in susceptibility to acute effects from nerve agents that inhibit cholinesterases.

Butyrylcholinesterase is thought to provide a normal protective mechanism whereby nerve agents, including pyridostigmine and organophosphate nerve agents, are “scavenged” and detoxified by chemical interaction with the enzyme. In support of this hypothesis, Loewenstein-Lichtenstein et al. (1995) reported that an Israeli soldier, who had experienced severe acute symptoms after taking pyridostigmine during the Gulf War, was found to have an ‘atypical’ butyrylcholinesterase that had a low potential to interact with pyridostigmine. Other support comes from animal experiments showing that the intravenous administration of acetylcholinesterase from fetal bovine serum or butyrylcholinesterase from human serum allows animals to survive, without toxic effects or neurobehavioral deficits, short-term exposures to a variety of organophosphate nerve agents at levels well above those that are normally lethal (see Wolfe et al., 1992).

It is unknown if individuals who have low levels of serum butyrylcholinesterase or who have ‘atypical’ butyrylcholinesterase will experience, after acute exposure to pyridostigmine or other nerve agents, delayed neurological impairments that are not experienced by others with normal

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1999); and examination of effects of low-level sarin, physical exercise, and pyridostigmine bromide on neurobehavioral, neurobiochemical, and neurophysiological variables in mice (DoD research project #62; RWG, 1999).

levels of typical butyrylcholinesterase. An ongoing exploratory research program at the University of Nebraska Medical Center (DoD research project #60, RWG, 1999) is comparing serum levels and genotypes of butyrylcholinesterase in healthy Gulf War veterans and Gulf War veterans who report chronic symptoms of ill health to determine if there are correlations between butyrylcholinesterase levels or genotype and generic chronic health symptoms associated with Gulf War service. A related ongoing project at the East Orange VA Medical Center is comparing neurobehavioral, physiological and biochemical responses to pyridostigmine, alone or in combination with physically-induced stress, in two strains of rats that differ in inherent serum levels of butyrylcholinesterase (DVA research project #49; RWG, 1999). This project is also examining if the amount of pyridostigmine that reaches the brain is different in the two strains of rats under conditions of repeated physically-induced stress compared with non-stress conditions.

In another ongoing exploratory program (DoD research project #51; RWG, 1999), a group at the Hebrew University of Jerusalem is genetically engineering mice to overexpress various types of cholinesterases in nervous tissue in an effort to understand genetic differences in susceptibility to nerve agents and to identify particular cholinesterase genotypes with the greatest potential to protect against acute toxicity from organophosphate nerve agents. In addition, this group is examining DNA from human subjects who display hypersensitivity to anti-cholinesterase agents, such as pyridostigmine, organophosphate insecticides, and organophosphate warfare nerve agents, in search of particular gene sequences that may correlate with hypersensitivity.

### ***Multiple Chemical Sensitivity in Gulf War Veterans***

Multiple chemical sensitivity is a hard-to-characterize disorder occurring in a subset of the general population in which individuals typically report a wide array of recurrent symptoms of ill health in response to very low concentrations of chemicals in the environment. Symptoms reported include fatigue, depression, headaches, gastrointestinal problems, muscle and joint pain, irritability, and memory and concentration difficulties (Miller, 1994). The biomedical community has not agreed on a case definition for this disorder due to several difficulties including the unreliability of self-reported symptoms linking illness to chemical exposure, the diversity of reported symptoms and their overlap with other illness such as chronic fatigue syndrome, post-traumatic stress disorder, and fibromyalgia, and the lack of a widely agreed upon diagnostic physical finding or test (Sorg et al., 1998; Bell et al., 1998a). The disorder has been proposed to occur following either long-term, low-level exposure or short-term, high-level exposure to chemicals. The underlying physiological basis of the disorder is not known, but several psychological, immunological, and biochemical mechanisms have been proposed (Miller, 1992, 1994; Buchwald and Garrity, 1994; Sorg, 1998; Bell et al., 1998a).

Fiedler et al. (1996) hypothesized that exposure to one or a combination of environmental agents during Gulf War service may be a contributing factor to health complaints in veterans with unexplained illnesses and that there may be a higher than expected prevalence of chronic fatigue syndrome and multiple chemical sensitivities among Gulf War veterans. Leading to this hypothesis was the observation that the most frequently reported symptoms among Gulf War

veterans with unexplained or undiagnosed illnesses in the DoD and DVA clinical programs<sup>41</sup> overlap with several of the required symptoms in the Center For Disease Control and Prevention's definition of chronic fatigue syndrome (fatigue, muscle/joint pain, headaches, and loss of memory; Fukuda et al., 1994), and are common in patients with multiple chemical sensitivities (Buchwald and Garrity, 1994).

A considerable prevalence of self-reported fatiguing illness and chemical sensitivities was found in a preliminary study that administered a questionnaire to a group of 432 Gulf War veterans who registered in the DVA Persian Gulf Health Registry; 203 previously listed fatigue as a medical complaint and 228 did not (Fiedler et al., 1996). Among those who initially reported fatigue and responded to the questionnaire: 89% reported that the fatiguing illness began in 1991 or 1992; 7% reported adopting three or more avoidance behaviors based on chemical sensitivities<sup>42</sup>; and 33% and 20% considered themselves especially sensitive to car exhaust and perfume, respectively. Among respondents who did not initially report fatigue, 63% reported developing fatiguing illness and 30% considered themselves sensitive to certain chemicals with 19% sensitive to car exhaust and 11% to perfume. A more extensive survey of 2800 registrants in the DVA Persian Gulf Health Registry is being conducted by this research group (DVA research project #5A; RWG, 1999). Ongoing analyses of these data (which include self-reported environmental exposures to chemicals) are examining potential associations among symptoms to define one or more case definitions of Gulf War unexplained illnesses and potential associations between environmental risk factors and symptoms.

In a small-scale telephone survey study, a statistically significant increased percentage of subjects who considered themselves especially sensitive to certain chemicals was found in ill Gulf-deployed veterans (12/14 subjects or 86%) compared with healthy Gulf-deployed veterans (3/10 or 30%), but not in ill non-deployed veterans (4/7 or 57%) compared with healthy non-deployed veterans (3/10 or 30%) (Bell et al. 1998b).

Although these studies (Fiedler et al., 1996; Bell et al., 1998b) suggest that chronic fatigue and chemical sensitivities are present among Gulf War veterans, they do not quantify the prevalence of these conditions among all Gulf War veterans because either the studied subjects do not represent a suitably large random sample of U.S. Gulf War veterans (both studies) or a control (non-deployed) group is not included. The importance of a control group to assess whether there is an increased prevalence of chemical sensitivities among Gulf War veterans is emphasized by results of past questionnaire studies of self-reported chemical sensitivity in other groups of people<sup>43</sup>

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<sup>41</sup> Fatigue, headache, memory problems, sleep disturbances, skin rash, joint pain, and shortness of breath.

<sup>42</sup> For example, following a special diet, wearing special clothes, taking special precautions in selecting home furnishings because of chemical sensitivities.

<sup>43</sup> Including college students, a rural population, office workers, and elderly WWII veterans.



showing that approximately 30% of subjects responded positively when questioned if they have chemical sensitivity and that only about 4-6% report chemical sensitivities severe enough to prompt drastic changes in their lifestyle (see Bell et al., 1998a,b). Although a larger scale study with a suitable questionnaire given to larger numbers of subjects representing random samples of all Gulf War veterans and non-deployed veterans from the same era may provide better information concerning prevalence of multiple chemical sensitivity, the lack of understanding of the neuropsychological and physiological basis of the condition itself may represent a more important problem to address with more research.

Research efforts to better understand physiological and neuropsychological characteristics in veterans reporting chronic fatigue and chemical sensitivities are ongoing at the East Orange, Tucson, and Boston VA Medical Centers, at Georgetown University (in collaboration with the Washington VA Medical Center), and at the University of Medicine and Dentistry of New Jersey. In general, it is believed that this research may lead to a better basis for proposing new methods of diagnosis and treatment of Gulf War veterans with unexplained chronic symptoms including chemical sensitivity.

- C At the East Orange Center, healthy veterans and veterans with chronic fatigue and/or chemical sensitivities have received comprehensive medical evaluations<sup>44</sup> and the results are being compared with civilians with chronic fatigue syndrome and/or chemical sensitivities (DVA research project #5B; RWG, 1999). A related research project is ongoing in which the effects<sup>45</sup> of short-term exposure to 5 ppm diesel exhaust and aerobic exercise are being compared in healthy veterans and veterans with chronic fatigue syndrome and/or chemical sensitivities (DVA research project #5C; RWG, 1998, 1999).
- C At the Tucson Center, several physiological and neuropsychological variables<sup>46</sup> will be measured in several groups of veterans following repeated exposure to controlled concentrations of jet fuel vapor or air (DVA research project #48; RWG, 1999). Subjects will include groups of ill Gulf War veterans with or without chemical sensitivity, healthy Gulf War veterans without chemical sensitivity, and healthy, non-deployed veterans of the Gulf War era.
- C At the Boston Center, in-depth neuropsychological evaluations that will diagnose multiple chemical sensitivity, chronic fatigue syndrome, post-traumatic stress disorder, and other related disorders have been given to groups of treatment-seeking Gulf War veterans and

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<sup>44</sup> Included were evaluations for viral infections and immune dysfunction, tests of neuropsychological variables, and tests of physiological responses to physical and cognitive challenges.

<sup>45</sup> Endpoints evaluated include self-reported symptoms, physiological responses such as heart rate and blood pressure, and performance in tests of cognitive ability.

<sup>46</sup> Endpoints will include blood pressure, heart rate, eyeblink and performance in tests of cognitive ability.

non-deployed veterans and groups of non-treatment seeking veterans (DoD research project #32; RWG, 1999). Analysis of collected data for over 300 subjects is ongoing and expected to have the potential to reveal differences between treatment-seeking deployed and non-deployed Gulf War-era veterans. A short questionnaire to identify multiple chemical sensitivity also has been developed (DoD research project #52; RWG, 1999). This will be used to compare prevalence of chemical sensitivities in female and male members of a cohort of Gulf War veterans and explore risk factors for the development of this condition.

- C At Georgetown University (in collaboration with the Washington VA Center), physiologic and biochemical variables<sup>47</sup> have been measured in Gulf War veterans with unexplained chronic symptoms, in civilian patients with chronic fatigue syndrome or fibromyalgia, and in healthy controls (DoD research project #31; RWG, 1999).
- C At the University of Medicine and Dentistry of New Jersey, the persistence of self-reported symptoms over time will be evaluated in a group of Gulf War veterans (DHHS research project #6; RWG, 1999). In addition, working definitions for multiple symptom illnesses, such as chronic fatigue syndrome and multiple chemical sensitivity, will be compared with alternative definitions as descriptors of unexplained illnesses in Gulf War veterans.

### ***Treatment of Gulf War Veterans with Non-specific Chronic Symptoms of Ill Health***

The DoD's Gulf War Health Center has a *Specialized Care Program* for people with persistent, non-specific symptoms associated with Gulf War service (Engel et al., 1998). This program is a 3-week outpatient treatment program involving three multidisciplinary teams of caregivers: a medical team, a physical team, and a psychosocial team. The program involves medical evaluations, exercise programs, therapy programs (e.g., physical, occupational, and recreational), and counseling. Patients are referred to this program after being evaluated in the DoD's Comprehensive Clinical Evaluation Program. A meta-analysis of studies of these types of programs for patients with chronic pain suggests they are useful in improving pain and mood, facilitating returning to work, and decreasing utilization of health care systems (Flor et al., 1992).

The DVA and DoD have established a 2-year, multiple-site, randomized control trial (starting in 1999 and ending in 2001) to compare treatment methods for U.S. Gulf War veterans who have unexplained chronic symptoms of pain, fatigue, and/or cognitive difficulties (DVA/DoD research project # 1D & 1V; RWG, 1999). Patients will be Gulf War veterans who are chronically experiencing at least two of the following self-reported symptoms: 1) fatigue that limits work, recreational, or social activity; 2) musculoskeletal pain in two or more body regions; and 3)

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<sup>47</sup> Variables include qualitative measures of general health symptoms, quantitative measures of pain and muscle motility, heart rate variability, levels of neurohormones in response to stress, and levels of neurotransmitters in cerebral spinal fluid.

difficulties in memory, concentration, or attention. The program will evaluate 339 randomly assigned patients in each of four treatment groups<sup>48</sup>: 1) “usual and customary care” (the control group); 2) cognitive behavioral therapy<sup>49</sup> plus usual and customary care; 3) aerobic exercise plus usual and customary care; and 4) cognitive behavioral therapy, plus aerobic exercise, and usual and customary care. Treatment will be in a group format and will last for 3 months (one hourly session per week for 12 weeks). Patients will be evaluated for physical function before and immediately after the end of treatment and at 6 and 12 months after start of treatment.

Limited research has investigated the possibility that some veterans with non-specific chronic symptoms may be infected with microorganisms that are difficult to detect and that treatment with antibiotics may be useful in alleviating symptoms (Nicolson and Nicolson, 1996; Nicolson et al., 1998; Nicolson, 1998; Hyman, 1996; See Appendix C for study details). Nicolson and Nicolson (1996) reported that mycoplasma gene sequences were detected in blood leukocytes from 14 subjects in a group of 30 Gulf War veterans with chronic symptoms similar to those associated with chronic fatigue syndrome and that 11/14 of these subjects recovered after multiple treatment cycles of antibiotics (doxycycline or ciprofloxacin). Nicolson et al. (1998) also reported that mycoplasma gene sequences were detected in blood leukocytes of 76 subjects in a group of 170 subjects comprised of Gulf War veterans with chronic-fatigue-syndrome-like symptoms and their immediate family members. Among 73 mycoplasma-positive subjects who received two to six 6-week cycles of antibiotic therapy (doxycycline, ciprofloxacin or azithromycin), 58 were reported to have recovered. Hyman (1996) reported detecting streptococcal bacteria remnants in urine of about ten Gulf War veterans who had chronic-fatigue-syndrome/fibromyalgia-like symptoms (and their immediate family members); treatment with antibiotics was reported to improve the health of the subjects initially, but most relapsed. Limitations of these studies include the lack of blind testing of the specimens, the lack of appropriate control groups, and the lack of investigation of a possible placebo effect (i.e., the lack of blinding of the subjects).

Further research is ongoing regarding the antibiotic treatment of Gulf War veterans with non-specific, chronic symptoms such as fatigue, difficulty concentrating, joint and muscle pain, and headache. The DVA has recently established a multiple-site, 30-month, double-blind clinical trial of antibiotic treatment of symptomatic patients with positive findings for mycoplasma infection (DVA research project # 55; RWG, 1999). The trial (to be conducted between 1999 and 2001) will identify 450 Gulf War veterans who are experiencing at least two of three chronic symptoms (fatigue, musculoskeletal pain, and neurocognitive dysfunction) and who are mycoplasma-positive. Subjects will be randomly assigned to 12-month treatments with either 300 mg

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<sup>48</sup> A total of 1356 patients.

<sup>49</sup> Cognitive Behavioral Therapy is a set of techniques that are based on psychological principles of behavioral conditioning (e.g., positive and negative reinforcement) and observational learning and are administered, with active patient participation, by a clinician trained in behavioral medicine. These techniques have been used in the treatment of physical problems such as low back pain, headaches, fibromyalgia (muscle pain), chronic fatigue, asthma, and arthritis (RWG, 1999).

doxycycline per day or placebo. Patients will be seen monthly during the medication phase and at 18 months. Physical function will be evaluated before treatment starts, and at 3, 6, 9, 12 and 18 months. Patients will also complete questionnaires designed to provide measures of pain, fatigue, and neurocognitive dysfunction.

Another project, funded by the DoD and conducted by the Louisiana Medical Foundation, involves blinded and placebo-controlled clinical trials of antibiotic treatment of patients who are experiencing chronic non-specific symptoms and who show bacterial remnants in their urine (DoD research project # 67; RWG, 1998; 1999). This trial is expected to be completed in 1999.

## **6. Concluding Remarks**

During the upcoming two-and-a-half day conference, participants from various disciplines will meet several times in workgroups with the goal of discussing and recommending research in one of four focus areas related to illnesses among Gulf War veterans:

- C Workgroup 1: Pathophysiology, Etiology, and Mechanisms of Action;
- C Workgroup 2: Assessment/Diagnosis;
- C Workgroup 3: Treatment; and
- C Workgroup 4: Prevention.

A central question to be addressed by Workgroup 1 is: What are the most plausible etiological hypotheses concerning 1) diagnosed diseases and 2) unexplained multiple-symptom illnesses noted among Gulf War veterans? Associated questions include: Are ongoing research projects addressing the most plausible of these hypotheses? If not, which additional plausible hypotheses should be addressed? Are there research methods or approaches that need to be developed, or that are available and not being used? The Gulf War experience has created interest in the health effects of particular chemical agents, such as depleted uranium, organophosphate chemical warfare nerve agents, carbamate prophylactic agents against organophosphate nerve agents, vaccines, and organophosphate pesticides. This interest leads to additional questions within the focus of Workgroup 1. Should additional research resources be applied to better understand exposure-response relationships for, mechanisms of actions of, individual susceptibility to, and/or biomarkers of exposure to specific chemical agents or classes of agents associated with the Gulf War experience? Are current research efforts to examine potential interactions among “Gulf war mixtures” of chemicals and other health risk factors of sufficient scope and design? What alternative research approaches could be taken to decrease the uncertainty that will exist in any future attempts to extrapolate results from the animal “mixtures” experiments to expected human exposure scenarios? Should such research efforts be made?

Results from several epidemiological studies concur that Gulf War veterans more frequently report multiple symptoms of ill health than non-deployed veterans of the same era and that there may be an increased frequency of chronic, multi-systemic conditions of ill health among groups of Gulf War veterans. The array of reported symptoms are, in general, difficult to diagnose into a disease category. The most frequently reported chronic symptoms among Gulf War veterans with

unexplained or undiagnosed illnesses in the DoD and DVA clinical programs (fatigue, headache, memory problems, sleep disturbances, skin rash, joint pain, and shortness of breath) and in epidemiology studies appear to overlap with several of the symptoms in other symptom-based disorders including chronic fatigue syndrome, fibromyalgia, and multiple chemical sensitivity. Using factor analysis to examine associations among self-reported symptoms in different sets of Gulf War veterans, one group of investigators proposed that there might be unique disorders among Gulf War veterans (Haley et al., 1997a,b; Haley and Kurt, 1997), whereas other groups concluded that evidence for a unique Gulf War syndrome was not found when control groups were included in the analysis (Fukuda et al., 1998; Ismail et al., 1999). These results are within the focus of Workgroup 2 and lead to several questions related to the goal of recommending research on the assessment and diagnosis of illnesses among Gulf War veterans. Are ongoing efforts to assess the prevalence of these and other illnesses among Gulf war veterans of sufficient scope and design? What are the best or optimal research approaches and methods to apply to the question of whether or not there are unique health conditions among Gulf War veterans? (i.e., are there Gulf War syndromes?) Are ongoing projects using these approaches and methods to address the issues of assessing and diagnosing illnesses among Gulf War veterans? Are there particular clinical and/or research methods or approaches that need further development or validation before they can be used to assess or diagnose illnesses among Gulf War veterans? Which of these methods or approaches hold the greatest promise in increasing the efficiency and accuracy of assessing and diagnosing illnesses among Gulf War veterans or veterans of future wars?

In response to the wide diversity of illnesses and symptoms experienced by Gulf War veterans and the uncertainty of their cause, several reviewers (Engel et al., 1998; Joseph et al., 1998; Lashof and Cassells, 1998) have noted that treatment should proceed on an individual basis and is best addressed when objective clinical measures of distinct illness can be made and that, in the absence of such measures, multidisciplinary treatment of symptoms may be effective. Questions of relevance to the focus of Workgroup 3 include: What are likely to be the most appropriate treatment and/or rehabilitation approaches for 1) veterans with the most frequently diagnosed categories of diseases and 2) veterans with unexplained multiple-symptom illnesses? Are ongoing clinical trials of treatment options (e.g., antibiotic treatment trials and multidisciplinary treatment trials) of appropriate scope, size, and design? Are there other potentially useful treatment approaches or methods that need more basic research before development? Is there a need to educate physicians concerning options in treating Gulf War veterans with illnesses? Are there sufficient health care opportunities for Gulf War veterans?

Joseph et al. (1988) have noted that the DoD has recognized recommendations from various scientific review panels and government agency groups of the need for improved health surveillance programs for military personnel before, during, and after deployment to combat situations, in order to decrease uncertainties regarding chronic, post-deployment health consequences. Components of the surveillance programs include enhancing capabilities of identifying individuals with health risks, conducting standardized health assessments before and after deployment, assessing and documenting exposures to hazardous substances through

environmental monitoring and/or biomonitoring, and monitoring health status of personnel after deployment (Joseph et al., 1988). Questions related to the focus of Workgroup 4, Prevention, include: How can health surveillance programs for U.S. military personnel be improved to decrease uncertainties about post-deployment health consequences? What types of health risk communication and education programs will be useful to prevent or minimize exposure to the most likely chemical and biological health hazards in future conflicts? What techniques or methods of environmental monitoring or biomonitoring are likely to be most useful in helping to prevent or minimize exposure to chemical or biological agents in future conflicts? Which of these require further research and development? What prophylactic methods are available against the most likely chemical and biological health hazards to be encountered in future conflicts? Which of these require further research and development?

Workgroups will meet for discussion and deliberation during four sessions of 2- to 3-hour duration. Final reports and recommendations from each Workgroup will be presented to the conference at large prior to adjournment.

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## APPENDICES

### Appendix A: Account of Events Related to Health Concerns of Gulf War Veterans

#### *Reporting of Gulf War Illnesses and U.S. Governmental Response*

During and after service in the Gulf War, some U.S. veterans began to experience adverse health effects. In April, 1991, while troops were still returning home, Congress passed legislation (Public Law [PL]102-25) requiring the Secretary of Defense and the Secretary of Veterans Affairs to:

- C assess needs for rehabilitative services for veterans experiencing PTSD, and describe programs and resources available to meet those needs ;
- C describe plans for treatment of veterans experiencing PTSD;
- C assess needs for additional resources to provide treatment; and
- C describe plans for coordination of treatment services for PTSD between the DoD and the DVA (IOM, 1996b).

In response to general concerns about possible health effects of exposure to oil well fires in the Persian Gulf, DVA established the PGHR in April, 1991 to provide clinical examinations for veterans concerned about illnesses that may be related to Gulf War service. This registry was later mandated in PL 102-585 as the DVA Persian Gulf War Veterans Health Registry, to include all U.S. military personnel who served in the Gulf. PL 102-585 also expanded previous legislation (PL 102-90 of December, 1991) to require that the DoD registry of troops exposed to burning oil well fires include all veterans who served in the Southwest Asia theater of operations during the Gulf War (IOM, 1996b). DVA's PGHR established referral centers in Washington, D.C., Houston, Texas, Los Angeles, California, and Birmingham Alabama. In June, 1994, DoD also started a CCEP for active duty troops modeled after DVA's referral center examinations (IOM, 1996b).

Concerns about unusual illnesses among Gulf War veterans arose initially through reports by individuals and then through "outbreak" studies of groups of soldiers who reported a high rate of a variety of nonspecific symptoms, including fatigue, joint pain and stiffness, disturbed or unrefreshing sleep, some gastrointestinal complaints, and a variety of complaints suggestive of mood and musculoskeletal disorders (IOM, 1996b; U.S. Senate, 1998). The set of nonspecific symptoms reported by Gulf War veterans, which also includes memory problems, shortness of breath, and impaired concentration, has not been associated with a characteristic set of clinical signs (Joseph et al., 1997; 1998). Estimates of veterans who reported illnesses possibly resulting from Gulf War service range from a few thousand within one to two years after the war, increasing to 49,000 by 1995 and more than 100,000 in 1997 (Joseph et al., 1998). There have also been concerns about possible occurrences of sudden death, various illnesses, and birth defects in children of veterans (Joseph et al., 1998).

## *Review Panels and Groups*

In response to White House and Congressional interest and involvement during initial actions undertaken by DVA and DoD, several committees and special groups were established to review, inspect, or evaluate various aspects of health issues related to Gulf War veterans. Following are descriptions of the work of some of these review groups.

In May, 1993, DVA convened a meeting of an informal panel of experts that was subsequently chartered as the *Persian Gulf Expert Scientific Committee* to advise the DVA about medical findings affecting Gulf War veterans. The committee was charged to:

- C review all aspects of patient care and medical diagnoses;
- C provide professional consultation as needed; and
- C advise on research and development, veterans benefits, and training for patients and staff.

The committee has had numerous meetings since its inception; the most recent meeting was in the spring of 1998.

In 1993, the DoD established a panel of non-governmental experts called the *Defense Science Board Task Force on Persian Gulf War Health Effects* to review:

- C all available intelligence and reports of chemical or biological agent detection or exposure during the Gulf War;
- C scientific and medical evidence relating to exposure to nerve agents at low levels and possible long-term effects; and
- C other potential health consequences resulting from low-level chemical exposure, environmental pollutants, Kuwaiti oil fires, endemic biologics or other health hazards attributed to Gulf War service.

The 1994 conclusions and recommendations of this group are briefly summarized as follows [see DSB (1994) for full report of findings, conclusions, and recommendations]:

- C there was no persuasive evidence that any of proposed etiologies caused chronic illness on a significant scale in the absence of acute injury at initial exposure;
- C there was “no scientific or medical evidence that either chemical or biological warfare was deployed” against U.S. forces or “that there were any exposures of U.S. service members to chemical or biological warfare agents in Kuwait or Saudi Arabia”;
- C the evidence, at the time of review, was insufficient “to support the concept of any coherent syndrome”, but research on veterans reporting a range of symptoms without a clear-cut diagnosis should be coordinated with ongoing studies of chronic fatigue syndrome in civilian populations;
- C more epidemiological research was needed to determine possible associations between health symptoms and any specific aspect of the Gulf War experience;
- C DoD, in coordination with DVA, “needs substantial improvements in pre- and post-deployment medical assessments and data handling”;



- C clinical treatment of Gulf War veterans with illnesses should be directed at the symptoms presented, and controlled treatment protocols “might assist in carving out specific syndromes from the broad range of symptoms noted”; and
- C further research is needed on the long-term health consequences of exposure to chemical or biological weapons, because of the possibility that these agents may be used in future wars.

In 1994, a National Institutes of Health (NIH) Technology Assessment Workshop, *The Persian Gulf Experience and Health*, was held, sponsored by the NIH Office of Medical Applications of Research, the Department of Health and Human Services, the DoD, the DVA, and the Environmental Protection Agency. Based on presentations and discussions at the workshop, a panel of non-government experts prepared a written statement in response to four key questions and arrived at five general conclusions as follows [see NIH (1994a,b) for the full statement of the workshop panel]:

- C “The complex biological, chemical, physical, and psychological environment of the Persian Gulf theater of operations appears to have produced complex adverse health effects in the primary military personnel.”
- C “No single disease or syndrome is apparent, but rather multiple illnesses with overlapping symptoms and causes. Some of these diagnoses or illnesses can be sorted out by rigorous diagnostic, medical, and epidemiological procedures. Others may only be characterized after further research is conducted.”
- C “A collaborative government-supported program has not been established. Evaluation of undiagnosed Persian Gulf illnesses has not followed a uniform protocol across military branches, VA facilities, and civilian physicians.”
- C “This has led to imprecise description of diseases and/or symptoms, uncertainties about underlying prevalence rates, and inconsistent treatments. Well-designed epidemiologic studies have not been conducted to link the illnesses of the military personnel with exposures in the Gulf theater of operations. The absence of such studies has hampered the development of an appropriate case definition.”
- C “Chronic symptoms of viscerotropic leishmaniasis and posttraumatic stress disorders were found to be compatible with some of the unexplained illnesses. The proportion of these illnesses attributable to leishmaniasis and PTSD is unknown at this time, however.”

PL 102-585 directed DVA and DoD to establish an agreement with the Institute of Medicine (IOM) of the National Academy of Sciences to review the collection and maintenance of data on health consequences of the Gulf War, consider reported health outcomes, and recommend appropriate studies. The IOM established several panels of experts: *the Committee to Review the Health Consequences of Service During the Persian Gulf War*; *the Committee on the Evaluation of the DoD Comprehensive Clinical Evaluation Program*; and *the Committee on the Evaluation of the Department of Veterans Affairs Uniform Case Assessment Protocol*. More recently formed IOM committees, whose work is ongoing, include the *Committee on Health Effects Associated with Exposures during the Persian Gulf War* (IOM, 1998a), and the *Committee on Measuring Health Status of Persian Gulf Veterans* (IOM, 1998b).

The IOM *Committee to Review the Health Consequences of Service During the Persian Gulf War* was established to:

- C review DOD and DVA efforts to collect and maintain health data on Gulf War veterans;
- C recommend improvements to the collection and maintenance of such data; and
- C recommend epidemiological research to be undertaken to better determine the health consequences of Gulf War service.

The committee published findings and recommendations in two reports (IOM, 1995; 1996a). In 1996, the Committee made 16 recommendations to the DoD and the DVA, summarized briefly as follows (see IOM (1996a) for full report of the committee's findings and recommendations):

- C establish uniform medical information systems that include an electronic medical record for each service person;
- C conduct studies to identify risk factors and develop better treatment methods for stress-related psychiatric disorders in military personnel;
- C conduct longitudinal follow-up studies of the mental health of Gulf War veterans, after peer-review of study methods;
- C improve military medical preparedness, for future deployments, to respond to physical and environmental exposures in the specific theater of operation;
- C support research to determine whether different or adverse health consequences are associated with reserves, National Guard, or regular troops;
- C compare the mortality experience of Gulf War-deployed veterans with non-deployed veterans for as long as 30 years;
- C conduct studies to discern the reasons for excess mortality from unintentional injury among Gulf War veterans;
- C evaluate and expand the Defense Medical Epidemiological Database;
- C complete development of information systems regarding unit locations during the Gulf War and environmental conditions;
- C assess the ability of troop-location information systems to evaluate troop health consequences;
- C ensure that studies of health effects of deployment evaluate gender-specific parameters;
- C conduct studies of health consequences of men and women serving together in the military;
- C complete and publish results of epidemiological studies conducted by the Naval Health Research Center, of the DVA National Health Survey, and of studies analyzing DVA PGHR data.
- C strengthen the epidemiological capabilities of the U.S. armed forces;
- C adopt a policy that results from DoD- and DVA-sponsored research be reported in a timely manner in the peer-reviewed scientific literature; and
- C publicly announce requests for research proposals related to Gulf War illnesses, and subject all proposals to review by panels of appropriately qualified experts.

In 1996, the IOM *Committee on the Evaluation of the DoD Comprehensive Clinical Evaluation Program (CCEP)* provided an overall assessment of the CCEP, and made numerous

recommendations to the DoD. The committee made the overall conclusion that “*the systematic, comprehensive set of clinical practice guidelines set forth in the CCEP are appropriate.*” The committee further concluded that *the interpretation that “the signs and symptoms in many patients can be explained by well-recognized conditions that are readily diagnosed and treatable” is a more likely interpretation of the information collected by the CCEP, than the interpretation that “a high proportion of the CCEP patients are suffering from a unique, previously unknown ‘mystery disease’.*” Selected recommendations to the DoD are briefly described as follows [see IOM (1996b) for full report of findings, conclusions and all recommendations]:

- C revise protocols to allow the majority of patients to receive a final diagnosis by Phase I;
- C continue referral of subgroups of patients whose illnesses are difficult to diagnose;
- C develop guidelines identifying Phase I patients who would benefit from psychiatric evaluation;
- C provide more detailed information on specific diagnoses in future reports;
- C do not view CCEP results as estimates of the prevalence of disability from Gulf War service;
- C there is a lack of clinical evidence of a unique “Persian Gulf Syndrome”;
- C improve standardization diagnostic criteria and provide more details in recording diagnoses (many specific recommendations for specific diagnostic categories were given and are not described herein);
- C continue ongoing, periodic public release of results of analysis of CCEP information;
- C compare and coordinate methods and clinical results of the CCEP with the DVA’s Uniform Case Assessment Protocol;
- C acknowledge the serious limitations of the CCEP data for epidemiological purposes; and
- C compare and contrast the types of health effects in individuals from special Gulf War units known to have special exposures to specific risk factors with health effects noted in other units.

In 1997, the IOM *Committee on the Evaluation of the DoD CCEP* evaluated the CCEP’s approach to diagnosing and treating subjects with low-level exposure to nerve agents, concluded that the CCEP provides “an appropriate screening approach to the diagnosis of disease” and made eight recommendations for improvement [see IOM (1997a) for full report of findings and recommendations]:

- C improve documentation of screening used in Phase I for patients with psychological conditions;
- C improve documentation of neurological screening done during Phases I and II of the program;
- C give Phase I primary physicians access to a neurologist and a psychiatrist for referral;
- C gather and record more complete patient health histories, including personal and family histories, and occupational and environmental exposure histories;
- C standardize, across the services, U.S. military pre-deployment physical examinations;
- C increase the uniformity of CCEP forms and reporting procedures across health facility sites;

- C provide written evidence, for each patient, that all organ systems were evaluated; and
- C offer group education and counseling to soldiers and their families about exposure to toxic agents.

In 1997 the IOM *Committee on the Evaluation of the DoD CCEP* made further recommendations to the DoD regarding the CCEP concerning [see IOM (1997b) for full report of findings and recommendations]:

- C diagnosis and treatment of medically unexplained symptom syndromes (e.g., chronic fatigue syndrome, fibromyalgia, and multiple chemical sensitivity);
- C collecting information about stress (i.e., traumatic events);
- C screening for depression and substance abuse;
- C evaluation of implementation of the CCEP across facilities; and
- C coordination with the DVA regarding ongoing treatment of patients and health care provider education.

The IOM *Committee on the Evaluation of the Department of Veterans Affairs Uniform Case Assessment Protocol* was established to:

- C evaluate the adequacy of the protocol to diagnose the broad range of medical assessment needs of Gulf War veterans;
- C evaluate implementation of the program, including the process for patient referrals;
- C evaluate VA outreach activities; and
- C evaluate VA provider education.

In 1998, the committee made eleven recommendations to the DVA, briefly summarized as follows [see IOM (1998d) for full report of the committee's findings and recommendations]:

- C adopt a new diagnostic pathway, at all VA facilities, eliminating the distinction between Phases I and II and including periodic reevaluation of patients without a diagnosis;
- C expand the initial evaluation of Gulf War veterans entering the registry program with new questions and tests recommended by a national panel of experts;
- C develop clinical practice guidelines for the most common symptoms among Gulf War veterans, and the difficult-to-diagnose, ill-defined, or medically unexplained conditions;
- C modify processes and procedures for specialty diagnosis and treatment;
- C establish an evaluation feedback mechanism to improve performance;
- C design and implement a patient-satisfaction questionnaire for Gulf War veterans;
- C improve the consistency of health data reporting across VA facilities;
- C develop a system to update individual patient information;
- C develop informational pamphlets addressing concerns of Gulf War veterans;
- C improve routine intake forms to more easily identify the war or conflict in which veterans served; and
- C encourage, and provide opportunities for, participation by Registry, primary-care, and specialist health care providers in education programs related to Gulf War health issues and problems.

In May, 1995, the President established a 12-membered panel, the *Presidential Advisory Committee on Gulf War Veterans' Illnesses* (PAC), to review multiple issues related to Gulf War Illnesses, including : research; coordinating efforts; medical treatment; outreach; external reviews; risk factors; and chemical and biological weapons.

The PAC (1996b; 1997) generally concluded that “the government largely had acted in good faith in handling Gulf War veterans’ health concerns in comparison to the post-Vietnam War era”, but “took strong exception, however, to the Department of Defense’s inquiries related to chemical and biological warfare agent investigations.” The PAC (1996a; 1996b; 1997) made numerous recommendations to the DoD and the DVA regarding: outreach programs for veterans with health concerns; medical and clinical policies, protocols, and education programs; research on Gulf War illnesses; investigations into possible chemical or biological warfare agents during the Gulf War; and development of an intraagency plan to address health preparedness for and readjustment of veterans and families after future conflicts and peace-keeping missions.

Regarding the possible causes of illnesses among Gulf War veterans, the PAC (1996b; 1997) concluded:

“current scientific evidence does not support a causal link between the symptoms and illnesses reported today by Gulf War veterans and exposures while in the Gulf region to the following environmental risk factors assessed by the Committee: pesticides, chemical warfare agents, biological warfare agents, vaccines, pyridostigmine bromide, infectious diseases, depleted uranium, oil-well fires and smoke, and petroleum products.” The PAC (1996b; 1997) acknowledged, however, that “some of these risk factors explain specific, diagnosed illnesses in a few Gulf War veterans, for example, leishmaniasis has been diagnosed in 32 individuals”, and that “Prudence requires further investigation of some areas of uncertainty, such as the long-term effects of low-level exposure to chemical warfare agents and the synergistic effects of exposure to pyridostigmine bromide and other risk factors.”

In response to a Presidential Advisory Committee recommendation, President Clinton, in 1998, created the Special Oversight Board for Department of Defense Investigations of Gulf War Chemical and Biological Incidents “to provide advice and recommendations based on review of DoD investigations into possible detections of, and exposures to, chemical or biological weapons agents and environmental and other factors that may have contributed to Gulf War Illnesses” (PSOB, 1998). This group held its first public hearing in November, 1998.

In November, 1997, the U.S. House of Representatives Committee on Government Reform and Oversight published a report of an investigation (initiated in March, 1996) into:

- C “the status of efforts to understand the clusters of symptoms and debilitating maladies known collectively as ‘Gulf War Syndrome’”;
- C the degree to which “Gulf War veterans were being diagnosed accurately, treated effectively and compensated fairly for service-connected disabilities”; and
- C “whether the Gulf War research agenda was properly focused on the most likely, not just the most convenient, hypotheses to explain Gulf War veterans’ illnesses.”

The committee made eighteen recommendations in four areas: diagnosis, treatment, compensation, and research [see U.S. House of Representatives (1997) for full report of the committee's findings and recommendations]. The five research recommendations were:

- C Congress should create or designate an agency independent from the Departments of Defense and Veterans' Affairs as the lead Federal agency responsible for coordination of all research into Gulf War veterans' illnesses and allocation of all research funds.
- C The lead Federal agency on Gulf War veterans' illnesses should focus research on the evaluation and treatment of the common spectrum of neuroimmunological disorders known as Gulf War Syndrome, multiple chemical sensitivity, chronic fatigue syndrome, and fibromyalgia.
- C DoD and DVA medical systems should augment research and clinical capabilities with regard to women's health issues and the health effects of combat service on women's health.
- C DVA, in collaboration with NIH, CDC, FDA, and other public health agencies should establish an interdisciplinary research and clinical program on the identification, prevention, and treatment of environmentally induced neuropathies.
- C FDA should grant a waiver of informed consent requirements for the use of experimental or investigational drugs by DoD only upon receipt of a Presidential finding of efficacy and need.

In 1997, The U.S. Senate Committee on Veteran Affairs established a staff of 20 experts and investigators, the *Special Investigation Unit on Gulf War Illnesses (SIU)*, to examine DoD's plans and policies, the intelligence community's role, health risks encountered by U.S. troops during the war, record keeping, and DVA's accountability to and responsibilities for Gulf War Veterans.

The SIU reviewed available written material, held hearings across the country, held site visits of DVA and DoD facilities, and met with government employees, veteran service organization representatives, health professionals, scientists, researchers, and Gulf War veterans and their families. The final report of the SIU was published recently (U.S. Senate, 1998). The SIU made four general recommendations:

- C "Preparedness shortfalls for effective defense against battlefield hazards existed before and during the Gulf War and continue today."
- C "Insufficient program monitoring hinders the Department of Defense's and Department of Veterans Affairs' effectiveness in serving Gulf War veterans."
- C The Department of Defense's and Department of Veterans Affairs' failure to collect information, retain records, and generate valid data analysis impedes effective responses to Gulf War veterans." and
- C "The Department of Defense and Department of Veterans Affairs must make ongoing cooperation and coordination a top priority to ensure timely and effective service for Gulf War veterans."

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## **Appendix B: Exposure to Chemicals During the Gulf War**

### ***Chemical Warfare Agents***

At the time of the Gulf War, the Iraqi forces had an experimental chemical weapons program and also had chemical munitions available for use in the field. United Nations Special Commission investigations indicated that chemical agents in the Iraqi chemical weapons program included sulfur mustard (a blistering agent), sarin, and VX (IOM, 1996b). Iraq was also assumed to have available the nerve agents, cyclosarin, soman, and tabun (CIA, 1997). The Iraqi's possession of munitions with nerve agents was well known. For example, in 1992, a U.K. newspaper, the Independent, reported that a United Nations demolition team announced they would destroy 400 sarin-filled, 122 mm rockets that were located at a large Iraqi weapons storage bunker, at Khamisiyah 25 miles north of Basra (Independent, 1992). It was reported that the bunker was damaged due to earlier Allied bombing raids and that it was necessary to blow up the rockets at the site because they were leaking.

In 1994, the U.S. Senate Committee on Banking, Housing, and Urban Affairs issued a report expressing the belief that there was "reliable evidence that U.S. forces were exposed to chemical and possibly biological agents" (U.S. Senate, 1994a). However, the 1994 National Institute of Health Technology Assessment Workshop report indicated that evidence of exposure to chemical warfare agents was controversial and drew no conclusions (NIH, 1994a,b). The Defense Science Board concluded that there was "no scientific or medical evidence" to indicate that U.S. troops in Kuwait or Saudi Arabia were exposed to chemical or biological warfare agents (DSB, 1994). In 1996, the Institute of Medicine (IOM, 1996b) indicated that there was no credible evidence that chemical weapons were used by Iraq in the Gulf War, noted that serious concerns persisted among veterans and some investigators that significant exposure to chemical agents may have occurred in non-combat situations, and pointed out that their committee had not had the opportunity to review evidence that troops may have been exposed to chemical agents during destruction of an Iraqi munitions bunker in March, 1991.

In response to inquiries from the Presidential Advisory Committee on Gulf War Veterans' Illnesses, the DoD announced in June 1996 that: chemical warfare agents had been known to be present at Iraqi weapons-storage sites at Khamisiyah, Iraq; that some of these sites were demolished by U.S. troops in March, 1991; and that troops in the vicinity may have experienced low-level exposure to chemical warfare nerve agents during the demolition events (PAC, 1996b; CIA, 1997; DoD, 1997a). The CIA (1997) acknowledged, based on information from United Nations Special Commission inspectors, that chemical warfare agents (sarin and cyclosarin) were likely present in at least two U.S. demolition events at Iraqi ammunition storage sites in the Khamisiyah area: one (Bunker 73) on March 4, 1991 and the other ("the pit") on March 10, 1991 (DoD, 1997a). DoD (1997a) noted that there was evidence that another demolition event occurred at "the pit" on March 12, 1991. In addition, chemical weapons storage sites at Muhammadiyat, and Al Muthanna, Iraq (northwest of Baghdad) were destroyed by Allied

bombing at the beginning of the Gulf War creating a potential risk of exposure for troops located 400-500 km south of the sites (RWG, 1997).

Because air monitoring data are not available for these events, models were developed, based on the limited amount of data available concerning the amount of nerve agent that may have existed at the Khamisiyah sites, to calculate estimates of ground level concentrations of nerve agents (sarin/cyclosarin) as a function of distance and direction away from detonation sites for the March 4 and 10, 1991 events (PAC, 1996b; CIA and DoD, 1997). Modeling results, as of October, 1996, indicated that exposure levels in the explosion plume within 25 kilometers of the demolition site may have been sufficient to cause runny nose, tightness in the chest and dimness of vision (CIA and DoD, 1997), but the U.S. Army Medical Corps reported to the PAC (1996b) that signs and symptoms characteristic of exposure to nerve agents such as sarin and soman were not seen by medical personnel during the Gulf War (PAC, 1996b), and no reports of distinct acute neurological poisonings during the March 1991 Khamisiyah demolitions were located. Efforts to decrease the uncertainty in the modeling efforts are ongoing (CIA and DoD, 1997). The PAC (1996b) concluded that evidence of chemical warfare agent release at Khamisiyah “is overwhelming” and that “low-level exposure to troops within a 50-km radius should be presumed while efforts to develop more precise measures of exposure and more detailed knowledge of the demolition activities continue.”

Beginning in August 1996, DoD notified approximately 20,000 individuals (those expected to have been within a 50-km radius of the Khamisiyah demolition sites) that they could have been exposed to low-levels of chemical warfare agents (DoD, 1997a; PAC, 1997). Surveys were mailed to these individuals concerning health symptoms that they recollected experiencing; the CIA and DoD (1997) reported that 7,400 responses were received and that 99 percent of responses indicated “no physical effects that could be correlated with exposure to sarin”. The PAC (1997) recommended that DoD should contact all individuals within a 300-mile radius of the Khamisiyah “pit”, notifying them if they are, or are not, expected to have been under the plume of the Khamisiyah demolition events.

The DoD has publicly released case narratives of investigations of numerous events of possible chemical warfare agent exposures during the Gulf War period. These include:

- C Czech and French detections of nerve gas and blister agents in January 1991 in the vicinities of Hafar al Batin and King Khalid Military City (DoD, 1998a),
- C chemical-agent detections by a Fox vehicle in an ammunition supply point in an orchard southwest of Kuwait City in February 1991 (DoD, 1997b),
- C reports of loud-noise, SCUD missile impacts, and “noxious” cloud events in the Al Jubayl, Saudi Arabia region on several dates between January and March, 1991 (DoD, 1997c),
- C several instances of suspected chemical warfare use during combat to retake Kuwaiti Air Base in Al Jaber in February, 1991 (DoD, 1997d),
- C multiple (18) chemical-alarm alerts reported by the 11<sup>th</sup> Marines over a 42-day period between January 17 and February 27, 1991 (DoD, 1998b),

- C reports of chemical weapon (mustard) storage at the Iraqi An Naisiriyah Southwest ammunition storage point, a site at which U.S. carried out demolition operations in March and April 1991 (DoD, 1998c), and
- C development of skin burns on a U.S. Army Sergeant after performing reconnaissance in an Iraqi bunker in March, 1991 (DoD, 1997e).

DoD investigators reached conclusions (noted as interim) regarding the possibility of exposure during these events that ranged from “definitely not” (Al Jubayl events; Al Jaber Air Base) to “likely” (Army Sergeant with mustard agent burns). Several events were assigned an “unlikely” assessment (11<sup>th</sup> Marine events; An Naisiriyah ammunition storage point; Fox detections in orchard). No narrative assigned the “definite” category of exposure assessment. The PAC (1997) recommended that an entity other than the DoD should provide oversight of investigations about possible chemical warfare agent exposures. The Presidential Special Oversight Board has been established to accomplish such a role (PSOB, 1998).

The PAC (1996a, 1997) noted that chemical-warfare-agent detectors used by the U.S. during the Gulf War period (e.g., M8A1 chemical agent alarms, Fox vehicles with MM-1 mass spectrometers, and other detectors) could detect nerve gas agents only at concentrations that would cause acute lethal or near-lethal poisonings and not at low levels that might have subclinical health significance. The principal battlefield detector (M8A1) could not detect mustard agent and was so non-specific in its detection that it was often ignored during the war. The PAC (1997) recommended that DoD support the development of new detectors for “low-level, subclinical exposures” to chemical warfare agents.

After review of information, data, and modeling calculations available for Khamisiyah and other sites, as well as DoD’s case narratives and information papers on the potential exposure of troops to chemical agents, the Senate’s Special Investigation Unit concluded that there was insufficient evidence to prove or disprove that there was an actual low-level exposure of any troops to chemical weapon nerve agents or that any of the health effects some veterans are experiencing were caused by such exposure (U.S. Senate, 1998).

### ***Pyridostigmine Bromide***

Pyridostigmine is an anti-nerve agent (a carbamate molecule) that binds reversibly at sites of the important nerve enzymes (cholinesterases) that are irreversibly bound by organophosphate nerve agents such as sarin. At suitable dosage levels, the binding of carbamates or organophosphates to cholinesterases causes an overstimulation of cholinergic nerves in the peripheral and central nervous systems. Pyridostigmine is expected to provide protection against severe acute organophosphate poisoning when given before exposure to organophosphate agents, based on results from animal experiments showing that pyridostigmine pretreatment coupled with post-exposure treatment with atropine and pralidoxime chloride increased survival after exposure to lethal concentrations of the nerve agent, soman (Harris et al., 1984; Dirnhuber et al., 1979). The reversible binding of pyridostigmine is thought to temporarily protect the enzymes from

permanent damage that can be caused by irreversibly binding organophosphate nerve agents (Glikson et al., 1991; Taylor, 1996).

Prior to the Gulf War, the U.S. Food and Drug Administration (FDA) had approved the use of this drug for the treatment of myasthenia gravis, an autoimmune disease characterized by muscle weakness, but had not approved its repeated use as a pretreatment, protective therapy against organophosphate nerve agents in healthy subjects (U.S. Senate, 1994b). FDA regulations require obtaining an informed consent agreement from any individual who might use such an “investigational new drug”. In 1990, the DoD requested that FDA waive its informed consent requirement for pyridostigmine, and, in January 1991, the FDA Commissioner agreed to waive informed consent due to the lack of an alternative satisfactory therapy against organophosphate nerve agents and the infeasibility of obtaining informed consent agreements under combat conditions (Annas, 1992; U.S. Senate, 1994b).

Although results from animal studies indicate that pretreatment with pyridostigmine is effective at decreasing lethality from certain organophosphate nerve agents (Dirnhuber et al., 1979; Harris et al., 1984), excessive doses of pyridostigmine are expected to cause some of the same acute toxic effects that are produced by organophosphate nerve agents due to stimulation of peripheral cholinergic nerves (Taylor, 1996). Studies with rhesus monkeys, however, showed that exposure to pyridostigmine at exposure levels that produced 70-80% inhibition of blood cholinesterase did not significantly affect performance in neurobehavioral tests, whereas exposure to the organophosphate agent, soman, at levels that produced similar blood cholinesterase inhibition, produced severe behavioral toxicity (Blick et al., 1994). These results suggest that the potency of pyridostigmine to affect the central nervous system is much less than the potency of organophosphate nerve agents. Recent results from rodent studies indicate that pyridostigmine pretreatment may not be equally effective at protecting against the lethality of all organophosphate nerve agents. Koplovitz et al. (1992) reported that pretreatment of mice or guinea pigs with pyridostigmine increased the efficacy of treatment with atropine and pralidoxime chloride after exposure to the organophosphate nerve agent, tabun, but with exposure to other organophosphate agents (sarin and VX), the efficacy of atropine and pralidoxime chloride treatment was decreased by pyridostigmine pretreatment.

DoD reported that all U.S. troops were supplied with pyridostigmine bromide pills, and that approximately 250,000 personnel took at least some pyridostigmine during the Gulf War (PAC, 1996b). During the Gulf War, pyridostigmine was to be used at the commanding officer’s judgement and was to be self-administered by individuals in 30-mg doses three times daily (U.S. Senate, 1998). At the recommended dosage levels, acute, transient “side effects” from pyridostigmine appear to be mild in most individuals who report experiencing them. Reports from U.S. medical personnel providing care to 41,650 U.S. soldiers who took the recommended dosage for 1 to 7 days in January 1991 indicated that about 50% experienced gastrointestinal symptoms, 5-30% experienced urinary urgency and frequency, <5% experienced headaches, runny nose or tingling of the extremities, 1% (483 soldiers) required clinical visitation, and <1% (28 soldiers) had to discontinue use due to severe acute reactions (Keeler et al., 1991).

There is evidence that stress may enhance the acute adverse effects from pyridostigmine treatment. Symptoms of central nervous system dysfunction (e.g., headaches, insomnia, drowsiness, nervousness, difficulties in focusing attention) were reported by about 24% of 213 soldiers who took pyridostigmine under wartime conditions and were surveyed within 24 hours, whereas in a double-blind, placebo-controlled study under non-stressed conditions, about 8% of subjects given the same dose of pyridostigmine bromide reported similar symptoms (Friedman et al., 1996). Friedman et al. (1996) hypothesized that stress may disrupt the blood-brain barrier in some manner, allowing greater quantities of pyridostigmine to enter the brain compared with quantities that enter under non-stress conditions.

At dosage levels used for organophosphate nerve agent protection, limited testing has suggested that the short-term use of pyridostigmine may not have delayed or chronic neurological effects. As noted above, pyridostigmine has been used widely for decades in the treatment of the autoimmune disease, myasthenia gravis. The muscle weakness and fatigue associated with this disease is due to an autoimmune reaction with the acetyl choline receptor in neuromuscular nerve junctions (Drachman, 1994; Taylor, 1996). In these diseased subjects, the ability of pyridostigmine to reversibly inhibit acetylcholinesterases is thought to sufficiently increase endogenous concentrations of acetyl choline so that the abnormally low numbers of functional acetyl choline receptors are stimulated and muscle function is improved. No reports were found of chronic neurological or psychological effects in myasthenia gravis patients chronically treated with pyridostigmine bromide. Animal studies have reported changes in structure, ultrastructure and electrophysiological properties of neuromuscular synapses after repeated exposures to carbamates similar in structure and activity to pyridostigmine (Engel et al., 1973; Hudson et al., 1978; Tiedt et al., 1978), but a double-blind, placebo-controlled study found no evidence for adverse effects in extensive tests of neuromuscular function in 35 healthy human volunteers who took 30 mg pyridostigmine bromide, three times a day for up to 8 days (Gliksion et al., 1991). In a study of 4 human volunteers who took 30 mg pyridostigmine bromide every 8 hours for 3 days, Borland (1985) reported that no drug-induced changes in electrical activity of the brain were detected and that acute reversible changes were noted in tests of visual motor coordination. The motor coordination changes were noted as minimal.

### ***Biological Warfare Agents***

At the time of the Gulf War, the Iraqi forces had experimental biological weapons programs and also had biological munitions available for use in the field. United Nations Special Commission investigations indicated that biological agents in the Iraqi biological weapons program included botulinum toxin, anthrax, aflatoxin, ricin, mycotoxins, hemorrhagic conjunctivitis virus, rotavirus, and wheat cover smut (IOM, 1996b). During the Gulf War, biological warfare agent field detectors were relatively primitive and could not be relied upon to accurately detect exposure in a timely fashion. U.S. Army hospital admission records identified one admission for anthrax, a disease indigenous to the Gulf region (PAC, 1996b; U.S. Senate, 1998).

Recent review panels (U.S. Senate, 1998; PAC, 1996b, 1997) have concluded that biological warfare agents were not likely used during the Gulf War because: there is no evidence to date from intelligence agencies that indicates their use; there were no verified detections of anthrax or botulinum toxin during the war; and examination of Iraqi soil samples and enzyme assays by U.S. laboratories did not find evidence of the presence of biological warfare agents.

As discussed previously, the Presidential Advisory Committee further recommended that, “To ensure credibility and thoroughness, further investigation of possible chemical or biological warfare agent exposures during the Gulf War should be conducted by a group independent of DoD.” (PAC, 1996b, 1997). The Presidential Special Oversight Board has been established to accomplish such a role (PSOB, 1998).

### *Infectious Diseases*

Many infectious diseases are prevalent in southwest Asia including, but not limited to, agents that cause diarrhea, leishmaniasis, sandfly fever, and malaria. DoD medical personnel monitored troops for the preceding diseases as well as for dengue fever, Sindbis, West Nile fever, Rift Valley fever, and Congo-Crimean hemorrhagic fever, and took measures to prevent illness from endemic diseases (Hyams et al., 1995; PAC, 1996b).

During the Gulf War, infectious diseases were not a significant problem; diarrhea was the most commonly reported condition. Occurrence of diarrhea was 4% per week early in the deployment and declined to <0.5% per week after controls on food sources were imposed (Hyams et al., 1995). Although sand fly fever had been a concern, no cases were found during the war (Hyams et al., 1995). Seven individuals with malaria were diagnosed, one individual had West Nile fever, and one death occurred from meningococcal meningitis (Hyams et al., 1995).

A small number of cases of leishmaniasis (a chronic disease transmitted, like sand fly fever, by the bite of the sand fly) has been diagnosed among U.S. Gulf War veterans: 12 cases of viscerotropic leishmaniasis and 19 cases of cutaneous leishmaniasis (PGVCB, 1995). Most of these cases have displayed objective signs of the chronic disease: elevated temperatures, lymphadenopathy, and hepatosplenomegaly (Magill et al., 1993). The PAC (1996b) arrived at the conclusion that it is unlikely that infectious diseases endemic to the Gulf are responsible for long-term health effects most frequently reported by Gulf War veterans.

Infections by mycoplasma species, microsporidia, and streptococcal bacteria have been hypothesized as possible explanations for illnesses noted in some Gulf War veterans. Nicolson and Nicolson (1996) reported that mycoplasma gene sequences were detected in blood leukocytes from 14 subjects in a group of 30 Gulf War veterans with chronic symptoms similar to those associated with chronic fatigue syndrome and that 11/14 of these subjects recovered after multiple treatment cycles of antibiotics (doxycycline or ciprofloxacin). Nicolson et al. (1998) also reported that mycoplasma gene sequences were detected in blood leukocytes of 76 subjects in a group of 170 subjects comprised of Gulf War veterans with chronic-fatigue-syndrome-like symptoms and

their immediate family members. Among 73 mycoplasma-positive subjects who received two to six 6-week cycles of antibiotic therapy (doxycycline, ciprofloxacin or azithromycin), 58 were reported to have recovered. Hyman (1996) reported the detection of streptococcal bacteria remnants in urine of about ten Gulf War veterans who had chronic-fatigue-syndrome/fibromyalgia-like symptoms (and their immediate family members); treatment with antibiotics was reported to improve the health of the subjects initially, but most relapsed. An initial DVA report of finding microsporidia in stool specimens of some Gulf War veterans was not confirmed with subsequent examinations of stool and gastrointestinal biopsy material (PAC, 1996b) or in CDC examinations of stool specimens from Gulf War veterans in Air Force units from Pennsylvania and Florida (Fukuda et al., 1998). In 1996, the PAC (1996b) expressed the belief that it was unlikely that these three infectious agents “are responsible for widespread disease among Gulf war veterans or their families.”

### ***Immunizations***

Seven vaccines (polio, diphtheria-tetanus, adenovirus 4 and 7, meningococcus A, CYW135, influenza, and measles-rubella) are administered to U.S. Army recruits during basic training, and others are administered upon deployment to high risk areas (hepatitis A and B, yellow fever, Japanese encephalitis, plague, rabies, and cholera) (IOM, 1996b). DoD reported to the PAC (1996b) that approximately 150,000 Gulf deployed personnel received at least one anthrax vaccination and about 8,000 personnel received at least one dose of botulinum toxoid vaccine, but adequate records to document which troops received the anthrax and botulinum toxoid vaccines were not available.

The anthrax vaccine, licensed by FDA since 1970, produces injection site reactions (e.g., swelling, tenderness) in about 6% of recipients (IOM, 1996b). The botulinum toxoid vaccine, which has been assigned an “investigational” status by the FDA and has been used as an investigational vaccine to protect high-risk laboratory workers, consists of five types of toxins (from *Clostridium botulinum*) that are converted to a “toxoid” status by reaction with formalin (IOM, 1996b). Annas (1992) has noted that the use of the vaccine in laboratory workers was discontinued in the mid-1970s before sufficient data on safety and efficacy had been collected for licensing purposes. The experience of the U.S. Army Medical Research Institute of Infectious Diseases with the botulinum toxoid vaccine indicates that transient reactions include pain, redness, and swelling at the injection site in about 10% of recipients, and headache, myalgia, fever, and malaise in about 3% (IOM, 1996b). Given the possibility that Iraq might use botulinum toxin as a biological weapon, the DoD had requested, in 1990, that FDA waive informed consent requirements for the use of a botulinum toxoid vaccine; this request was granted by the FDA in 1991 noting that obtaining informed consent agreements was not feasible under combat conditions (U.S. Senate, 1994b). Annas (1992) reported that the DoD sent a letter to the FDA noting that, during the Gulf War, the military command decided to administer the botulinum toxoid vaccine on a voluntary basis.

## *Depleted Uranium (DU)*

DU, a byproduct of uranium refinement, is a very dense material that is used to increase the penetration capability of antitank munitions and as a protective shield on tanks against enemy fire (DoD, 1998d). The major toxicity of acute exposure to DU is from its chemical properties, rather than its radioactive properties, but there is uncertainty regarding toxicity from long-term exposure (IOM, 1996b). DU, which has about half the radioactivity of natural uranium, was first used in combat during the Gulf War, during which U.S. troops fired approximately 285 tons of DU munitions. Many U.S. troops handled munitions containing DU, but significant exposure with handling is not expected since the DU is encased in a protective shell (IOM, 1996b). Radiation exposure from intact DU munitions and armor is minimal and within accepted standards of health safety (GAO, 1993; IOM, 1996b).

During the Gulf War, friendly fire incidents wounded 35 U.S. soldiers of whom 22 were suspected to have retained DU fragments. Thirty-three of these wounded soldiers are undergoing a DVA-sponsored medical surveillance program at the Baltimore VA Medical Center. After 3 years, 15 of the 33 soldiers had detectable shrapnel. To date, the follow-up studies have found no evidence for neurological, renal, genotoxic, or immunological effects, but uranium excretion has been noted to be elevated in those known to have retained shrapnel (Keogh, 1995; Joseph et al., 1998). A report of the findings of this surveillance program is in preparation and will likely be available in 1999 (DVA, 1999).

The PAC (1996b) and the GAO (1993) noted that DoD had appropriate procedures for protecting personnel who worked with DU contaminated vehicles during the Gulf War but, apparently, few U.S. service personnel were adequately trained in these procedures. Activities of the 144<sup>th</sup> Service and Supply Company in fighting fires, recovering vehicles, and cleaning 29 tanks damaged by DU munitions may have led to DU exposure of 27 soldiers. Results of testing 12 of these soldiers were negative and the remaining 15 chose not to be tested (IOM, 1996b). Another two dozen soldiers from the 24<sup>th</sup> Infantry Division have reported that they were unknowingly exposed to DU-contaminated debris in the course of vehicle recovery and maintenance operations (PAC, 1996b). Additionally, troops may have inhaled particles containing DU while working near a fire at the Doha-Kuwait armored vehicle depot, or while climbing onto allied or enemy vehicles that had been hit by munitions containing DU (U.S. Senate, 1998).

DoD (1998d) classified possible DU exposures during the Gulf War into three levels:

- C Level I represents immediate and direct exposures of soldiers in or near combat vehicles at the times these vehicles were struck by DU penetrators or who entered vehicles immediately after they were struck by DU munitions. These soldiers could have been struck by DU fragments, inhaled DU aerosols, ingested DU residues, or had DU particles land on open wounds, burns, or other breaks in their skin.
- C Level II represents a lower level of exposure for soldiers and a small number of DoD civilian employees who worked in and around wrecked vehicles containing DU fragments and particles. These people may have inhaled DU residues resuspended during their



activities, transferred DU from hand to mouth, or spread contamination on their clothing. This Level includes soldiers who were involved in cleaning up DU residues that remained after a motor pool fire in which DU munitions detonated and burned.

- C Level III represents people who received short-term and very low exposures and included individuals who entered DU-containing Iraqi equipment, troops downwind from burning Iraqi or U.S. equipment struck by DU rounds, or personnel downwind from burning DU ammunition.

DoD (1998d) identified thirteen exposure events during the Gulf War period - two classified as Level I, seven as Level II, and four as Level III. Health risk assessments are being prepared for all thirteen events. The risk assessments will describe the activities of the participants, specify the sources of potential DU exposure, and estimate the dose from inhalation, ingestion, and wound contamination as appropriate for each exposure (DoD, 1998d).

In 1998, the DoD and DVA expanded a medical follow-up program conducted by the Baltimore VA Medical Center to evaluate the remaining veterans who received the largest DU exposures during the Gulf War, those involved in Level I and II exposure events. The evaluations will include a medical examination, determination of uranium levels in the urine, and completion of a detailed DU exposure questionnaire (Rostker, 1998; DVA, 1998b).

### *Pesticides*

The DoD reported that pesticides shipped to the Gulf region for use during the war included 45,770 pounds of malathion, 8,410 pounds of chlorpyrifos, 1,858 pounds of D-phenothrin, 903 pounds of methomyl, and 539 pounds of lindane (IOM, 1996b). Pyrethrin, dichlorovos (DDVP), carbaryl, propoxur, and diazinon were also available but in amounts less than 330 pounds each (IOM, 1996b). All pesticides shipped were approved by EPA or FDA for general use in the United States at the time of the war (PAC, 1996b). It is not known how much of this inventory of pesticides was actually used or what troop exposures may have resulted (IOM, 1996b).

The use of pesticides in the Gulf was reported to have followed strict guidelines. They were used only after arthropod surveys that identified individual pests and estimated arthropod prevalence. Distribution of pesticides was prohibited unless approved by the local commander. Distribution or use for other than personal purposes was restricted to trained or certified personnel or contractors (IOM, 1996b).

DoD reported that about 2.2 spray-cans of permethrin and 2 tubes of DEET (33%) for each U.S. service member were shipped to the Gulf (PAC, 1996b). Some troops were reported to have both applied the insect repellents DEET on their skin and permethrin on their clothing between August and October, 1990, the peak occurrence of arthropods (IOM, 1996b). In addition, some service personnel chose to wear animal flea collars for protection from insects, although DoD discouraged this practice (U.S. Senate, 1998).

## *Smoke from Oil Well Fires*

Near the end of the Gulf War in February, 1991, the Iraqi troops set more than 1,000 Kuwaiti oil wells and refineries on fire (Spektor, 1998). The burning wells were located in eastern Kuwait, with the majority to the south of Kuwait City. Smoke plumes rose and combined in a “superplume” that could be seen for hundreds of kilometers and sometimes even partially blocked out the sun (U.S. Senate, 1998).

Systematic environmental monitoring did not begin until May 1991, so limited exposure data are available for the period when most U.S. troops were in the Gulf area (Spektor, 1998, USAEHA, 1994). The U.S. Army’s Environmental Hygiene Agency (USAEHA) carried out the largest monitoring effort, collecting nearly 4,000 ambient air and soil samples between May and December, 1991 (USAEHA, 1994).

Air monitoring data from the USAEHA and other U.S. and international agencies indicated that air levels of nitrogen oxides, carbon monoxide, sulfur dioxide, hydrogen sulfide, other pollutant gases, and polycyclic aromatic hydrocarbons (PAHs) were lower than anticipated and did not exceed levels seen in urban air in a typical U.S. industrial city (USAEHA, 1994; Spektor, 1998). A health risk assessment conducted by the USAEHA (1994) based on the air monitoring data for volatile organic compounds, particulate heavy metals, and PAHs predicted an excess risk for cancer of three cases per million persons exposed. Risks for non-cancer health effects were estimated by a hazard index approach comparing estimated exposure levels during the fires to U.S. EPA reference exposure levels expected to be without adverse health effects (an index greater than 1 indicates increased risk for general populations including sensitive individuals): hazard indices ranged from 0.6 to 2.0 in Saudi Arabia and 2.0 to 5.0 in Kuwait (USAEHA, 1994).

Inhalation of volatile organic chemicals, particularly benzene, contributed to over 99 percent of the non-cancer health risk at all monitoring sites. The USAEHA (1994) noted that the EPA reference exposure levels each have at least 10-fold margins of safety incorporated in their derivation and that hazard indices in the range of 1 to 10 should not present “an unreasonable health risk, particularly for short-term exposures”, noting that DoD personnel were exposed to the smoke for a minimum of about a month to a maximum of about 9 months.

Etzel and Ashley (1994) found elevated concentrations of several volatile organic compounds (VOCs) in blood samples collected from 40 American firefighters working in the Kuwait oilfields in October, 1991 compared with blood levels in a random sample of 114 U.S. residents. The measured VOCs (benzene, toluene, xylene, and styrene) are components of smoke from oil well fires; blood levels in firefighters were about two times average levels in the reference group. Concentrations of these VOCs were not elevated, however, in blood collected in May 1991 from 14 U.S. personnel who worked in Kuwait City compared with reference levels.

Analyses of biologic samples from deployed troops, local inhabitants, and autopsy cases have not indicated a risk for health effects from atmospheric pollution caused by the fires (Coombe and Drysdale, 1993; Mullick, 1996). No cases of illness with symptoms resembling the most prevalent

symptoms reported by U.S. Gulf War veterans in the DoD and DVA health registries have been found in a group of 110 oil-well firefighters who worked daily at Kuwaiti wells in 1991 for 28-day periods without breathing-protection equipment or in other oil-well firefighters with years of experience (Friedman, 1994, 1996).

One study reported an increase in frequency of sister-chromatid exchange in blood cells collected from soldiers who were deployed from Germany to the Persian Gulf to participate in monitoring of the Kuwait oil-well fires between June and September, 1991 (after combat had ceased), but the cause of this apparent increase could not be determined (McDiarmid et al., 1995). Sister chromatid exchanges have been used as an indicator of exposure to a number of environmental mutagenic agents, including polycyclic aromatic hydrocarbons (PAHs). PAHs and other mutagenic agents are present in smoke from oil-well fires and from other fires as well. A further study of a subset of these soldiers measured levels of three biomarkers for exposure to PAHs (two measures of PAH-DNA adducts in blood cells and urinary levels of 1-hydroxypyrene-glucuronide, a metabolite of PAHs) before deployment to the Gulf, during deployment in Kuwait (after 8 weeks of duty), and 4 weeks after returning to Germany (Poirer et al., 1998). Levels of PAH biomarkers were lowest during deployment in Kuwait, suggesting that this group of soldiers were not exposed to elevated levels of PAHs while deployed in Kuwait.

### ***Petroleum Products and Other Chemicals***

The fuel used most widely during the Gulf War for both vehicles and equipment was Jet A-1, a kerosene-based aviation fuel. Of the 1.8 billion gallons of fuel used during the Gulf War, roughly 75 percent was jet fuel (mostly Jet A-1), 24 percent was diesel fuel, and 1 percent was gasoline. The gasoline was commercial leaded gasoline (PAC, 1996b). About 145,000 gallons of gasoline were used per day for eight months starting in August, 1990 (IOM, 1996b). Besides use in vehicles and machine engines, petroleum products were used to burn human waste and trash and as a fuel in stoves (U.S. Senate, 1998). Diesel fuel was used in large amounts to suppress dust, with one reported case involving 30,000 gallons used on roads daily. Troops living in tents near the roads, and particularly truck drivers who carried out the spraying, complained of nausea from breathing the resulting fumes (PAC, 1996b).

When fuels were used for heaters, cooking stoves, and portable generators, the fumes and exhaust produced by these fuels, particularly when used in unventilated tents, would have exposed some service members to benzene, toluene, xylene, ethyl benzene, and combustion products including carbon monoxide, sulfur dioxide, nitrogen dioxide, particulates, lead, and other pollutants (PAC, 1996b; U.S. Senate, 1998; IOM, 1996b). Air and limited blood monitoring found no evidence of elevated exposure to volatile organic compounds (PAC, 1996b). A recent study simulated Gulf War exposures to aerosols from unvented heaters in tents and found elevated concentrations of particulate matter, nitrogen oxides and carbon monoxide (Cheng, 1998). Fuel type, heater type, and air exchange rate were important factors in determining air concentrations in the tent. Cheng (1998) noted that information from this study will be used to calculate respiratory doses that may

have been experienced by troops residing in heated tents during the Gulf War and to calculate estimates of health risks from this type of exposure.

Chemical Agent Resistant Coating (CARC) paint, which releases a compound (toluene diisocyanate) that can adversely affect the lungs, was applied to vehicles and equipment before shipment to the Gulf area or at a port in Dhahran (U.S. Senate, 1998). Accidental exposure to a chemical decontaminant agent containing propylene and ethylene glycols reportedly caused rashes in a group of soldiers (U.S. Senate, 1998).

### ***The Desert Environment***

In the initial months of the deployment, troops were exposed to summer daytime temperatures that reached as high as 130 degrees Fahrenheit. In August and September, the mean high temperatures were approximately 100 degrees Fahrenheit with very intense solar heat and low humidity. Preventive medicine efforts resulted in very few heat casualties (U.S. Senate, 1998; Joseph et al., 1998). In surveillance data on 40,000 Marines, less than three cases of heat injury requiring aid station treatment occurred weekly per 1,000 people (U.S. Senate, 1998). Sand flies were present, as evidenced by a few cases of leishmaniasis (IOM, 1996b).

High levels of airborne particulates were detected at several monitoring sites in the Gulf theater and sample analysis indicated that, frequently, the particulates were predominately sand (USAEHA,1994). Korenyi-Both et al. (1992, 1997) theorized that acute respiratory problems experienced by U.S. troops in Al Eskan village between January and March, 1991 were caused as a result of immunosuppression from inhalation of airborne fine sand particulates along with organic pathogenic components; it was further theorized that the acute event may have induced a later-developing state of immunodeficiency that may be related to symptoms of ill health reported by Gulf War veterans. Studies to test this hypothesis were not located.

### ***Psychological and Physical Stressors***

The stresses of the Gulf War experience, some of which were unique, included sudden mobilization for military service in a hot, sandy, and foreign desert; exposures to the largest, most dramatic oil well and refinery fires in history, which spilled smoke and oil over a vast area; and potential exposure to chemical and biological warfare agents. Stresses reported by a group of over 2,000 Gulf War veterans as they returned home included nearly 300 events they considered stressful beyond the traditional combat experiences. The reported stress-related events were grouped into the following categories (U.S. Senate, 1998):

- C Combat and mission stressors such as actual threat to life from missiles (e.g., friendly fire incidents) or direct exposure to another's death or injury as part of a combat mission.
- C Non-combat war-zone stressors such as a unit member seriously injured or killed in a non-mission accident.

- C Domestic stressors such as divorce or long separation from or illness of family members and loved ones.
- C Anticipation of war/combat activities related to missile attack alerts or fear of attack by chemical or biological agents.
- C Physical attributes of the war zone such as severe climate or environmental conditions, long tours of duty, physical limitations and dangers from wearing chemical protective gear in a desert environment, or uncertainty about the war's duration.
- C Intra-unit stress related to personal conflicts in a unit, leadership failure or problems, or harassment.

Stress from personal and family concerns likely played a more prominent role in the Gulf War than in other wars, because it involved a greater number of married personnel and parents. In the Vietnam War, 16% of those deployed were married with children, whereas 60% of service members and reservists in the Gulf War were married with dependents, including approximately 32,000 single parents who had to make arrangements for their children during the deployment (U.S. Senate, 1998).

### ***General Exposures of Military Service***

In the military environment, personnel are required to perform multiple combat and non-combat activities that may involve potentially hazardous exposures, some of which may be similar to those in the civilian workplace. In addition, however, military personnel who participate in combat and combat support operations are exposed to inherent hazards that are associated with the operation of weapons systems and the battlefield environment. Common exposures to risk factors in the combat environment include propellants from ammunition; combustion products from vehicles; solvents; chemical warfare agents; noise, vibration, and non-ionizing radiation from communications and radar tracking equipment and laser target designators; blast impact, acoustical energy, airborne toxicants, extremes in barometric pressure, oxygen deficiency, and whole-body vibration from operation of tanks, aircraft, and submarines; biological hazards; extremes in temperature, humidity, and weather; and psychological stressors related to fear and isolation. Since a large proportion of the Gulf War veterans were members of the reserves or National Guard and also had non-military jobs, their civilian occupational exposures are potential confounders in the evaluation of their health problems (Joseph et al., 1998).

Hyams et al. (1996) noted that the clinical findings for Gulf War veterans are consistent with the experiences of U.S. veterans of previous wars. Reviewing U.S. clinical reports of war-related illnesses associated with the Civil War, World Wars I and II, the Korean Conflict, and the Vietnam War, Hyams recognized two general categories of war-related illnesses that were diagnosed after each of these wars:

1) psychological illnesses, given various names through the years from *nostalgia* in the Civil War, through *shell shock* in WWI, and *battle fatigue* in WWII and Korea, to *post-traumatic stress disorder* after the Vietnam and Gulf Wars; and

2) physiological illnesses, including *Da Costa* syndrome (irritable heart) after the Civil War, *Effort syndrome* during and after WWI and II, *Agent Orange exposure* after Vietnam, and *Gulf War syndrome*.

The physiological illnesses were primarily defined by self-reported, chronic symptoms including fatigue, shortness of breath, headache, sleep disturbances, impaired concentration, and forgetfulness. Hyams noted that these symptoms are non-specific and are frequently found in all adult populations, as well as among persons with illnesses associated with psychological stress, and that, in each of these wars, the onset of these illnesses was preceded by a high frequency of diarrhea. Hyams concluded that “poorly understood war syndromes” have recurred since the U.S. Civil War, that no single disease or underlying cause that is unrelated to psychological stress is apparent from reviewing the available clinical reports, and that the relationships between chronic, non-specific symptoms and physiological and psychological illness need to be better understood.

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## **Appendix C: Research on Gulf War Illnesses: Description and Evaluation of Selected Studies**

### ***Mortality and Hospitalization Studies***

[Writer, J.V., R.F. DeFraités, J.F. Brundage. 1996. Comparative mortality among US military personnel in the Persian Gulf region and worldwide during Operations Desert Shield and Desert Storm. JAMA. 275: 118-121.]

Writer et al. (1996) determined cause-specific mortality rates during the Gulf War period (August 1, 1990 through July 31, 1991) for U.S. troops deployed to the Persian Gulf (n = 688,702) and compared them with rates for U.S. troops deployed elsewhere during the same period (n = 2,590,193). Standardized mortality ratios (SMR) of age-adjusted mortality rates (deployed ÷ non-deployed x 100) and their 95% confidence intervals (95% CI) were calculated for specific causes of death. During the study period, Persian Gulf troops did not experience statistically significantly higher non-battle-related mortality rates than U.S. troops serving elsewhere, except for deaths from unintentional injury (SMR [95% CI]: 154.3 [132.0-176.7]). In the deployed troops, deaths associated with motor vehicles and aircraft accounted for about one-third and one-quarter, respectively, of deaths from unintentional injury.

[Kang, H.K. and T.A. Bullman. 1996. Mortality among U.S. veterans of the Persian Gulf war. N. Engl. J. Med. 335: 1498-1504.]

Kang and Bullman (1996) determined cause-specific mortality rates for a 2-year period after deployment [May 1, 1991 through September 30, 1993] for U.S. troops deployed to the Persian Gulf between August 1990 to April 1991 (n = 695,516) and compared them with rates for a stratified random sample of U.S. troops (active duty, National Guard, and military reserves) deployed elsewhere between September 1990 and April 1991 (n = 746,291). To compare these groups, SMRs (and 95% CIs) were calculated after adjusting mortality rates for branch of service, type of unit, age, sex, and race. A small, but statistically significant, excess of deaths from all causes was found for the deployed troops compared with the non-deployed troops (SMR = 109 [1.01-1.16]). SMRs for death from diseases (e.g., cancer, circulatory disease, or infectious or parasitic diseases) were not significantly elevated in the deployed troops, but significantly elevated SMRs were found for “all external causes” (1.17 [1.08-1.27]), “all accidents” (1.25 [1.13-1.39]), and “motor vehicle accidents” (1.31 [1.14-1.49]). Cause-specific mortality rates for either group of military personnel were consistently lower than rates for the general U.S. population, in concordance with a “healthy soldier” effect that is analogous to the healthy-worker effect observed in occupational studies. Elevated SMRs for external causes of death were found for women in the deployed (n = 49,919) group, compared with the general U.S. population, but the elevation was not statistically significant (SMR = 1.14 [0.84-1.52]).

[Gray, G.C., B.D. Coate, C.M. Anderson, H.K. Kang, S.W. Berg, F. S. Wignall, J.D. Knoke, E. Barrett-Connor. 1996. The postwar hospitalization experience of U.S. veterans of the Persian Gulf War. *N. Engl. J. Med.* 335: 1505-1513.]

Gray et al. (1996) compared military hospitalizations of 547,076 Gulf War-deployed and 618,335 non-deployed regular-service active-duty U.S. military personnel in 14 diagnostic categories for a period before the war and for two years after the war. Gulf War veterans were defined as those who served in the Gulf War for one or more days between August 8, 1990 and July 31, 1991. Active duty personnel were studied since they are rarely hospitalized in non DoD facilities. The comparison group of active duty, non-deployed personnel was selected randomly, except that the number of subjects selected from each service branch was proportional to the number sent to the Gulf War. The Gulf War veterans were disproportionately younger and male compared with other veterans serving in the same era; accordingly, the hospitalization and rate ratios were adjusted for age and sex. Two years before the Gulf War, those who subsequently served in that war were at slightly lower risk of hospitalization than other veterans. To control for the selection bias that resulted from deploying only the healthiest soldiers in the Gulf War, the analytical models included a covariate representing prewar hospitalization. Because of high attrition from military service after the Gulf War (due primarily to military downsizing) and the subsequent loss of follow-up, hospitalizations that occurred after September 30, 1993 were not studied. Multivariate logistic-regression models were used to analyze risk factors for hospitalization both overall and in 14 diagnostic categories (excluding diagnoses involving the reproductive system) under the International Classification of Diseases (ICD-9) system during three periods (the last five months of 1991, the entirety of 1992, and the first nine months of 1993). In each period, a subject was counted only once with regard to each diagnostic category. The overall odds ratio for hospitalization of Gulf War veterans after the war was not elevated compared with other veterans.

In an analysis that included only troops that remained on active duty for at least half of the period studied, Gulf War veterans were at greater risk than other veterans in five categories: neoplasms in 1991, diseases of the genitourinary tract in 1991, diseases of the blood and blood-forming organs in 1992, and mental disorders in 1992 and 1993 (Gray et al., 1996). The odds ratios for these categories were only slightly elevated (the maximum odds ratio was approximately 1.1 based on examination of Figure 2 in the published report) and were not consistently observed across all periods. Analysis of hospitalization rates for specific neoplasms indicated a higher standardized rate ratio (RR) for malignant neoplasms of the testis for Gulf War veterans compared with other veterans [RR = 2.12 (1.11-4.02, 95% CI)] during 1991, but not for the 1992 [RR = 1.39 (0.91-2.11)] or 1993 [RR = 0.89 (0.54-1.44)] periods. RRs for specific genitourinary system disorders were elevated during 1991, but not in 1992 or 1993. The significantly elevated RRs for specific genitourinary disorders during 1991 were: for inflammatory diseases of the ovary, fallopian tube, pelvic cellular tissue, and peritoneum [RR = 1.35 (1.11-1.63)] and for infertility [RR = 1.59 (1.19-2.11)], in female Gulf War veterans; and for redundant prepuce and phimosis [RR = 1.59 (1.22-2.07)] in male Gulf War veterans. In the 1992 period, for which an elevated odds ratio for diseases of the blood and blood-forming organs was calculated, the most

common diagnosis was for anemia. The most frequent diagnoses for the mental disorder categories were related to alcohol or other drug abuse. In summary, these analyses found elevations in risk of hospitalization for certain diagnostic categories among Gulf War veterans compared with other veterans that were not consistent across the time periods studied; thus, the findings did not clearly suggest an emerging pattern of illness in this population of Gulf War veterans.

Limitations of the Gray et al. (1996) study include:

- C the study population, while large, was not a representative sample of illness in all Gulf War veterans, since it included only DoD hospitalizations of regular service, active-duty personnel (non-military hospitalizations or non-hospitalized illnesses were not included);
- C the study could not detect illnesses in active-duty personnel who left the service during the period, or in Gulf War veterans who served in reserve or National Guard units;
- C the study design could not detect possible associations between illnesses and geographically- or temporally-specific exposures experienced during the Gulf War;
- C the study period was limited to a 2 and a half year period after the war; diseases with longer latency periods (e.g., many types of cancer) would not have been detected;
- C some subjects had minimal exposure to elements of the Gulf War environment (the study population included subjects deployed to the Gulf for as little as one day); and
- C the study relied on assignment of patients to ICD-9 diagnostic categories; elevated rates for a new or poorly recognized disease syndrome may not have been detected due to misclassification.

[Knoke, J.D. and G.C. Gray. 1998. Hospitalizations for unexplained illnesses among U.S. veterans of the Persian Gulf War. *Emerging Infectious Diseases*. 4: 211-219.]

Knoke and Gray (1998) compared post-war military hospitalization rates for diagnoses consistent with an *unexplained illness* in Gulf War deployed and non-deployed active-duty U.S. military personnel. Hospitalization records for a 4.67-year period (August 1, 1991 through March 31, 1996) were examined for 552,111 Gulf War-deployed regular-service veterans and 1,479,751 non-deployed veterans of the same era, who were on active duty for one or more days during the Gulf War period (August 8, 1990 through July 31, 1991) and retained active-duty status during the whole study period. Knoke and Gray defined an *unexplained illness* as any one of 77 ICD-9 diagnoses used by the Emerging Infections Program of the CDC to monitor death certificates for unexplained deaths; these diagnoses primarily relate to nonspecific infections (of various organ systems) and ill-defined conditions. A Cox proportional hazards model approach was used to adjust hospitalization rates for an unexplained illness for several selected covariates including categories of deployment, race, gender, military rank, and prewar hospitalization status. Deployed veterans, compared with non-deployed veterans, showed a significantly, but slight, elevated rate ratio [RR = 1.06 (1.03-1.09, 95% CI)] for hospitalization rate for an unexplained illness. When the deployed subjects who were CCEP participants were censored from the analysis, the rate ratio for hospitalization for an unexplained illness in the deployed group was no

longer elevated [RR = 0.93 (0.91-0.96)]. Knoke and Gray noted that the CCEP participants were censored, because most were hospitalized for evaluation only and not for clinical management.

Strengths of the Knoke and Gray (1998) study include the large numbers in the study population, the likelihood of few missing values since most active-duty personnel exclusively use DoD hospitals, and the relative reliability of hospital discharge as a measure of illness compared with patient report. These strengths also apply to the Gray et al. (1996) study. Limitations of the study include the first four limitations noted previously in this report for the Gray et al. (1996) study, except that the study period was lengthened to 4.67 years. Knoke and Gray (1998) also noted that some miscoding of Gulf War deployment status was evident and that the collection of diagnoses used to define unexplained illnesses was not designed specifically for the purposes of the study.

[Knoke, J.D., G.C. Gray, G.C. Garland. 1998. Testicular cancer and Persian Gulf War service. *Epidemiology*. 9: 648-653.]

Knoke et al. (1998) compared post-war military hospitalization rates for testicular cancer in Gulf War deployed and non-deployed active-duty U.S. military personnel. First admissions into DoD hospitals across a 4.67-year post-war period (August 1, 1991 through March 31, 1996) with a principal diagnosis of testicular cancer were reviewed among 517,223 male Gulf War-deployed regular service veterans and 1,291,323 non-deployed male veterans of the same era who were on active duty for one or more days during the Gulf War period (August 8, 1990 through July 31, 1991). All admissions with a secondary diagnosis of testicular cancer, but not a primary diagnosis, were also reviewed. There were 134 and 371 cases of testicular cancer among the deployed and non-deployed groups, respectively. A Cox proportional hazards model approach was used to adjust hospitalization rates for testicular cancer for several selected covariates including categories of deployment, race, military rank, age, and occupation. Rate ratios for hospitalization for testicular cancer in the deployed veterans compared with the non-deployed group were not significantly elevated for the total study period [RR = 1.05 (0.86-1.29)]. Probabilities of hospitalization from testicular cancer were also calculated for the deployed and non-deployed groups and examined as a function of follow-up time. This analysis showed that the deployed group had a greater risk than the non-deployed group in the early months after the war, that this increased risk persisted (but did not accelerate) for about 3 years, and that the risk was not increased by the end of the 4.67-year follow-up period. Knoke et al. (1998) speculated that the early apparent difference between deployed and non-deployed hospitalization rates for testicular cancer may have been associated with deferred medical attention during the war. Strengths and limitations of this study are similar to those previously discussed for the other Naval Health Research Center studies (Gray et al., 1996; Knoke and Gray, 1998). The limited follow-up period of 4.67 years is of particular note for a late-developing disease such as cancer. Knoke et al. (1998) noted that a survey approach will likely be required for further follow-up because of the rate of separation from active duty.

[Penman, A.D., R.S. Tarver and M.M. Currier. 1996. No evidence of increase in birth defects and health problems among children born to Persian Gulf War Veterans in Mississippi. *Mil. Med.* 161: 1-6.]

Anecdotal reports of increased birth defects among Gulf War veterans have been reported in the popular press; a local Jackson Mississippi newspaper reported an apparent cluster of birth defects in the infants of National Guardsmen deployed in the Persian Gulf. To document this apparent cluster, Penman et al. (1996) examined medical records of 54 of 55 children born after Gulf region deployment to 52 veterans of the two Mississippi National Guard units with the presumed birth defects cluster. The study was designed to include live births and stillbirths, but no stillbirths were reported by the veterans. The study authors concluded that the frequency of minor and major birth defects, premature births, low birth weight, and other health effects in infants appeared to be similar to reported U.S. general population rates although it does not appear that the comparisons were statistically analyzed. Interpretation of these results is confounded by the small sample size and the apparent lack of statistical analysis.

[Cowan, D.N., R.F. DeFraitess, G.C. Gray, M.B. Goldenbaum and S.M. Wishik. 1997. The risk of birth defects among children of Persian Gulf War veterans. *New. Engl. J. Med.* 336: 1650-1656.]

Larger scale reproductive outcome studies were subsequently conducted by Cowan et al. (1997) and Aranata et al. (1997). In the Cowan et al. (1997) study, the prevalence of birth defects was examined in children of male and female Gulf War veterans (active duty in the Persian Gulf for at least one day from 8 August 1990 to 31 July 1991) and children of military personnel not deployed to the Gulf region. Medical records were examined for live births occurring in military medical treatment facilities during 1991, 1992, and 1993. Infants were included in the study if the parent(s) were active duty personnel, the births occurred before 1 October 1993, and conception occurred after the veterans returned from the Gulf region (for non-deployed personnel, the births occurred after 31 December 1990 and before 1 October 1993). No positive association between Gulf War service and the risk of birth defects were found among the 30,151 infants of male Gulf War veterans, as compared to 29,468 children of non-deployed male veterans. The risk of birth defects was slightly elevated among the 3,847 infants of female Gulf War veterans, as compared to 8,825 infants of non-deployed female veterans; the relative risk was 1.12 with 95% confidence intervals of 1.00 and 1.25. This increased risk appears to be the result of confounding by race or ethnicity, marital status, and branch of service since the relative risk was no longer statistically significant after adjustment for these variables. Additionally, the risks of severe birth defects or altered sex ratio were not significantly altered in the male or female veterans, and no relationship between risk and length of time in the Gulf region were found. Examination of only live births limits the ability of the study to conclude whether there is an association between Gulf War deployment and increased risk of birth defects because it does not record the prevalence in stillbirths or whether a pregnancy was terminated due to malformations. The Gray et al. (1996) hospitalization study used a similar study design and thus, the previously discussed limitations would also apply to the Cowan et al. (1997) study.



[Aranata, M.R.G., C.A. Moore, R.S. Olney, et al. 1997. Goldenhar syndrome among infants born in military hospitals to Gulf War veterans. *Teratol.* 56: 244-251.]

Using a similar design, Aranata et al. (1997) examined the prevalence of Goldenhar syndrome in 34,069 infants of Gulf War veterans and 41,345 infants of military personnel not deployed to the Gulf region. All births occurred before 1 October 1993 at military treatment facilities, the parents were still on active duty, and the infants were conceived after the veteran returned home from the Gulf region (for the non-deployed veterans, the births occurred after 31 December 1990). This study focused on Goldenhar syndrome because it was one of the congenital malformations described in the popular press reports. Goldenhar syndrome is characterized by abnormal prenatal development of facial structures; some of the features can include ear anomalies such as microtia, anotia or preauricular tags, asymmetry or hypoplasia of the face or mandible, unilateral epibulbar dermoids, colobomas of the upper lids, vertebral anomalies, and lateral facial clefts. Two pediatricians blinded to Gulf War status, examined the medical records, subsequent hospital admissions, and genetic evaluations of all infants diagnosed with an anomaly of the skull and facial bones and infants diagnosed with selected defects associated with Goldenhar syndrome. Although a higher prevalence of Goldenhar syndrome was found among the Gulf War veterans (5 versus 2 in non-deployed veterans; relative risk of 3.03 and 95% confidence interval of 0.63-20.57), the difference was not statistically significant.

### ***Mortality and Hospitalization Studies Summary***

In summary, the Naval Health Research Center's studies of hospitalization rates (Gray et al., 1996; Knoke and Gray, 1998; Knoke et al., 1998) have not found consistent evidence for increased rates of hospitalizations during a 4.67-year post-war period among Gulf War-deployed, active-duty, regular-service U.S. military personnel, compared with a referent group of non-deployed U.S. military personnel. The study populations in these studies were of sufficient size to statistically detect small differences in hospitalization rates, but, as discussed previously, several limitations shared by the studies prevent drawing any definitive conclusions regarding hospitalization rates during the same period for all U.S. Gulf War veterans.

The three available reproductive-outcome studies provide suggestive evidence that there is not a higher risk of birth defects among Gulf War veterans. However, these studies do not provide conclusive evidence due to design limitations including small sample size, inclusion of live births only, and the limited scope of the endpoints examined. Several ongoing studies (as described by Cowan et al., 1998) will hopefully address some of these limitations. These include studies examining: 1) births among separated and active duty personnel in military and civilian hospitals in seven states, 2) reproductive outcomes in a nationwide sample of veterans, 3) health of female veterans, and 4) birth defects in the children of British Gulf War veterans.

### ***Critique of Mortality and Hospitalization Studies***

[Haley, R.W. 1998a. Point: Bias from the “health-warrior effect” and unequal follow-up in three government studies of health effects of the Gulf War. *Am. J. Epidemiol.* 148: 315-323; Kang, H.K. and T. Bullman. 1998. Counterpoint: negligible “healthy-warrior effect” on Gulf War veterans’ mortality. *Am. J. Epidemiol.* 148: 324-325; Gray, G.C., J.D. Knoke, S.W. Berg et al. 1998. Counterpoint: Responding to suppositions and misunderstandings. *Am. J. Epidemiol.* 148:328-333; Cowan, D.N., G.C. Gray, R.F. DeFraités. 1998. Counterpoint: Responding to inadequate critique of birth defects paper. *Am. J. Epidemiol.* 148: 326-327; Haley, R.W. 1998b. Countercounterpoint: Haley replies. *Am. J. Epidemiol.* 148: 334-338.]

Haley (1998a) published a joint critique of the Kang and Bullman (1996) mortality rate study, the Gray et al. (1996) hospitalization rate study, and the Cowan et al. (1997) study of rates of birth defects in offspring of groups of veterans similar to those studied in the Gray et al. study. Haley (1998a) contended that the studies were biased toward finding no excess risk in deployed veterans because of: errors in calculation of confidence intervals; lack of adjustment for selection bias between deployed and nondeployed troops; and exclusion of nonmilitary hospitalizations. In reply, Kang and Bullman (1998) argued that the calculational adjustments would make no practical differences and that there was not a selection bias as noted by Haley. Gray et al. (1998) provided arguments that Haley’s criticisms were based on faulty suppositions and misunderstandings of methodology and military population characteristics. Cowan et al. (1998), in reply to Haley, acknowledged that their study and other published studies of reproductive outcomes do not prove that there is no increased risk of birth defects among Gulf War veterans, but questioned the usefulness of further research in this area, in the absence of “a clearly defined hypothesis regarding measurable exposures and specific birth defects”, if ongoing studies also find no positive evidence. Final responses in the debate were provided by Haley (1998b) who maintained that the three studies should be retracted and reanalyzed. Readers are referred to issue No. 4 of the *American Journal of Epidemiology* for the full commentaries.

### ***Studies of Self-Reported Symptoms in Gulf War Deployed and Non-Deployed Veterans***

[CDC (Centers for Disease Control and Prevention). 1995. Unexplained illness among Persian Gulf War veterans in an Air National Guard unit: Preliminary report -- August 1990-March 1995. *MMWR.* 44: 443-447.]

Late in 1994 and extending into 1995, CDC conducted an evaluation of Gulf War veterans in response to reports of unexplained illnesses among members of an Air National Guard (ANG) unit in south-central Pennsylvania (Unit A) (CDC, 1995). These veterans had reported symptoms that included rash, diarrhea, and fatigue at a local VA medical center. The purpose of CDC’s evaluation was to 1) verify and characterize the signs and symptoms and 2) determine the prevalence of the signs and symptoms among members of Unit A deployed and not deployed to the Gulf, and also relative to members of other units; a third objective was to characterize the illness and identify associated risk factors; results from the third objective were presented in a

subsequent report (Fukuda et al. 1998). Comparison units were chosen for similarity in mission responsibility to Unit A and were located in Pennsylvania and Florida. Fifty-nine Gulf veterans reported to be symptomatic. Their median age was 39 years and 50 were male; all were enlisted personnel. The most frequently reported symptoms considered “moderate” or “severe” were fatigue (61%), joint pain (51%), nasal or sinus congestion (51%), diarrhea (44%), joint stiffness (44%), unrefreshing sleep (42%), excessive gas (41%), “difficulty remembering” (41%), muscle pains (41%), headaches (39%), abdominal pain (36%), general weakness (34%), and impaired concentration (34%). The symptoms reportedly began 2-3 months after departure from the Persian Gulf and persisted for 6 months. Standardized physical examination or review of medical records and accompanying laboratory tests performed at the VA medical center revealed no consistent abnormalities among the participants. Members from Unit A as well as from the three comparison units were asked to complete a questionnaire describing the frequency, duration, and severity of 35 symptoms most commonly mentioned during the first phase of the investigation and a general health history. Also, personnel who had served in the Persian Gulf were asked to provide data regarding possible exposures scenarios. A total of 3,927 personnel participated in the survey and response rates varied among units from 36% to 78%. The results of the analysis showed that in all units, the prevalence of each of 13 chronic symptoms (lasting 6 months) was significantly greater among subjects deployed to the Gulf than among those not deployed. Moreover, the prevalence of five symptom categories, chronic diarrhea, other gastrointestinal complaints, difficulty remembering or concentrating, “trouble finding words”, and fatigue were significantly greater among deployed personnel from Unit A than among deployed personnel from other units. The prevalence of symptoms among non-deployed personnel was similar across units. The authors of the CDC (1995) evaluation indicated that their preliminary findings are subject to at least two limitations. First, the fact that the symptom prevalence reflected self-reported information not evaluated by physical examination and laboratory tests and, second, participation rates may have been biased towards selection of persons with symptoms leading to overestimation of prevalence of health conditions.

[Fukuda, K., R. Nisebaum, G. Stewart, W.W. Thompson, L. Robin, R.W. Washko, D.L. Noah, D.H. Barrett, B. Randall, B.L. Herwaldt, A.C. Mawle, W.C. Reeves. 1998. Chronic multisymptom illness affecting Air Force veterans of the Gulf War. *JAMA*. 280: 981-988.]

The results of a more complete evaluation of the cohorts examined by the CDC (1995) were recently published (Fukuda et al. 1998). This evaluation included a clinical study in which the subjects were classified as cases or noncases based on their responses to the mailed clinical epidemiological questionnaire. A major objective was to develop a case definition that captured the chronic multi symptomatic nature of illnesses in Gulf War veterans. The cross-sectional clinical evaluation included 158 Gulf War veterans (from 667 in the index unit who completed the questionnaire), irrespective of health status. The clinical case definition was identified as fatigue, difficulty remembering or concentrating, moodiness, difficulty sleeping, joint pain, and joint stiffness. A case was defined as having one or more chronic symptoms from at least 2 of 3 categories (fatigue, mood-cognition, and musculoskeletal). The clinical evaluation included psychiatric screening, physical examination, clinical laboratory tests, and serologic assays for

antibodies against viruses, rickettsia, parasites, and bacteria. The results showed a substantially higher prevalence of symptoms among Gulf War veterans than non-deployed veterans. The prevalence of mild-to-moderate and severe cases was 39% and 6%, respectively, among 1,115 Gulf War veterans compared with 14% and 0.7%, respectively, among 2,520 non-deployed personnel. Illness was not associated with time or place of deployment or with duties during the war. Fifty-nine clinically-evaluated veterans (37%) were noncases, 86 (54%) mild-to-moderate cases, and 13 (8%) severe cases. Although no physical examination, laboratory, or serologic findings identified cases, veterans who met the case definition had significantly diminished functioning and well being. A major limitation of this study, as stated by the authors, is the fact that it involved currently active duty air force personnel and cannot be generalized to other branches of service or to Gulf War veterans who have left the service. In addition, the symptoms were self-reported and may have been subject to reporting or recall bias. The finding that 15% of non-deployed also meet the case definition suggests that the multi symptom illness observed in this population is not unique to Gulf War service.

[Iowa Persian Gulf Study Group. 1997. Self-reported illness and health status among Gulf War veterans: A population-based study. *JAMA*. 277: 238-245.]

The Iowa Persian Gulf Study Group (1997) assessed the prevalence of self-reported symptoms and illnesses among Iowa Gulf-deployed veterans and compared these rates with those among Iowa non-Gulf-deployed military personnel. The study population consisted of 28,968 persons from which 4,886 were randomly selected from one of four study domains: Gulf-deployed regular military, Gulf-deployed National Guard/Reserve, non-Gulf-deployed regular military, and non-Gulf-deployed National Guard/Reserve. Of these 4,886 subjects, 3,695 completed a telephone interview, which was used as the means for assessing relevant medical and psychiatric conditions. Within each study domain, the population was further stratified by age, sex, race, rank, and branch of service. This resulted in 64 potential strata within each of the four study domains. The specific medical and psychiatric conditions investigated in the study were defined clearly prior to the development of the survey instrument and were based on answers to multiple questions and using accepted criteria from standardized instrument and the medical literature. Telephone interviews were conducted approximately five years after the Gulf-deployed. The relationship between each major medical and psychiatric condition and each category of exposure type were assessed using the Cochran-Mantel-Haenzel  $\chi^2$  test. Compared to non-deployed military personnel, Gulf-deployed military personnel reported a significantly higher prevalence of symptoms of depression (17% vs 10.9%), posttraumatic stress disorder (1.9% vs 0.8%), chronic fatigue (1.3% vs 0.3%), cognitive dysfunction (18.7% vs 7.6%), bronchitis (3.7% vs 2.7%), asthma (7.2% vs 4.1%), fibromyalgia (19.2% vs 9.6%), alcohol abuse (17.4% vs 12.6%), anxiety (4.0% vs 1.8%), and sexual discomfort (1.5% vs 1.1%). In addition, assessment of health-related quality of life showed lower mental and physical scores for Gulf-deployed personnel than for non-deployed personnel. Possible explanations for the findings discussed by the authors included a distinct cause of exposure being responsible for each of the self-reported medical and psychiatric conditions; one specific psychiatric condition, such as depression, representing the primary medical condition associated with the Gulf War; exposures or prophylactic measures may have

acted synergistically with other exposures encountered in military settings causing more severe disease; Gulf War military personnel developed a multisystemic condition that does not fit well into an established category of disease; and the reported medical and psychiatric conditions among Gulf War veterans may have not been unique to the Gulf War. A final possibility discussed by the authors was that of differential recall between deployed and non-deployed personnel. Limitations of the study discussed by the authors included the fact that the study population comprised only subjects with a home record of Iowa, differential participation by selected demographic subgroups, lack of internal validation of the responses in the telephone interview, limited analysis done to compare rates of self-reported medical and psychiatric conditions among the subjects in different study domains, lack of statistical control for the number of comparisons required in the study, and no objective physical or laboratory validation of the self-reported symptoms.

[Stretch, R.H., P.D. Bliese, D.H. Marlowe, K.M. Wright, K.H. Knudson, C.H. Hoover. 1995. Physical health symptomatology of Gulf War-era service personnel from the states of Pennsylvania and Hawaii. *Military Medicine*. 160: 131-136; Stretch, R.H., P.D. Bliese, D.H. Marlowe, K.M. Wright, K.H. Knudson, C.H. Hoover. 1996a. Post-traumatic stress disorder symptoms among Gulf War veterans. *Military Medicine*. 161: 407-410; Stretch, R.H., P.D. Bliese, D.H. Marlowe, K.M. Wright, K.H. Knudson, C.H. Hoover. 1995. Psychological health of Gulf War-era military personnel. *Military Medicine*. 161: 257-261.]

Stretch et al. (1995) studied the effects of the Gulf War on active duty, National Guard, and reserve units in Hawaii and Pennsylvania. The evaluation was conducted by means of a questionnaire that provided self-report information on demographics, physical health symptomatology, and general psychological health. Approximately 16,167 survey questionnaires were distributed with a gross return of 31%. The subjects responded anonymously. The cohort consisted of 715 active duty and 766 reserve veterans who deployed, and 1,576 active duty and 948 veterans who did not deploy. A comparison of the percentages of both active duty deployers and non-deployers who indicated that they had experienced any of 23 physical health symptoms within the past months showed that deployed veterans reported significantly more physical health symptoms than non-deployed veterans. Similar results were found among reserve veterans. Controlling for smoking and drinking did not significantly alter the outcome of the comparisons. The differences between deployed and non-deployed veterans persisted after controlling for demographic variables such as age, rank, education, marital status, and branch of military service. The major conclusion regarding physical health was that for those who deployed to the Gulf War and currently reported physical symptoms, neither stress nor exposure to combat or its aftermath bear much relationship to their physical distress; only the fact of deployment differentiated them from those with less self-reported symptoms. Subsequent studies of this cohort by the same group of investigators showed that while deployers and non-deployers had modest differences in psychological outcomes (deployers exhibit more stress), deployment to the Gulf War did not result in any significant increases in psychological distress relative to other military personnel who did not deploy to the Gulf (Stretch et al. 1996b). The authors also reported that deployed active duty and reserve personnel had an increased likelihood of developing posttraumatic stress

disorder symptoms than non-deployed veterans (Stretch et al. 1996a). These two more recent studies also made use of the survey questionnaire methodology. The relative low participation rate in these studies obscures the significance of the results.

[Wolfe, J., S.P. Proctor, J.D. Davis, M.S. Borgos, M.J. Friedman. 1998. Health symptoms reported by Persian Gulf War veterans two years after return. *Amer. J. Ind. Med.* 33: 104-113.]

A recent study by Wolfe et al. (1998) investigated the possible association between opportunities for exposure and increased rates of health symptoms reporting among Gulf War veterans. The cohort consisted of subjects from the Ft. Devens ODS Reunion Survey, a longitudinal study of U.S. Army Active, Reserve and National Guard soldiers who deployed to the Gulf during 1990-1991. The study was conducted 18-24 months post-return. Of 2,313 subjects surveyed, 2,119 completed a questionnaire; nonrespondents were more likely to be on active duty status and African-American. Specifically, the authors examined the association between proxies for three wartime experiences (reported exposure to poison gas or germ warfare, being in a transportation unit, or high levels of combat exposure) and health symptoms reports after adjusting for background characteristics (i.e., gender, psychological distress). For the overall cohort, the five most commonly endorsed health symptoms on the health symptom checklist were in decreasing prevalence; aches/pains, lack of energy, headaches, insomnia, and feeling nervous and tense. In a final multivariate regression analysis, reported exposure to poison gas significantly predicted increased reports of health symptoms. Veterans who belonged to a transportation unit also were at increased risk, but the odds ratio was not significantly greater than 1. Those with higher combat exposure were not more likely to report increased health symptoms. In all models, PTSD symptomatology was significantly associated with high health symptom endorsement. However, when those with presumptive PTSD were excluded from the analysis, those who reported exposure to poison gas remained at higher risk for reporting a high number of health symptoms. The health findings in this study are consistent with those of other studies, and so are the limitations. Among the latter, the authors mention the fact that the study relied on cross-sectional data, no pre-deployment health data, exposure recall may have been affected by the time elapsed between exposure and data collection and by recall bias.

[Pierce, P.N. 1997. Physical and emotional health of Gulf War veteran women. *Aviation, Space Environ Med.* 68: 317-321.]

In a general health study by Pierce (1997), 484 female Air Force (active duty, reserve, or guard) veterans were asked to complete self-administered health questionnaires; the initial questionnaire was completed approximately 2 years after the war and the follow-up questionnaire was completed 2 years later (4 years after the war). The cohort consisted of 153 of the veterans deployed to the Persian Gulf region (74 and 79 were deployed in the region for less than 120 days and greater than 120 days, respectively) and 331 veterans deployed elsewhere. The general health questionnaire consisted of a list of specific symptoms which the respondent indicated the frequency of the symptoms during the last 12 months. Two years after the war, there was a statistically significant increase in the frequency of insomnia among the veterans deployed for less

than 120 days, as compared to the non-deployed veterans. The frequency of self-reported depression was also higher in this group, although no difference was found in the results of standardized measures of depression. In the veterans deployed in the Gulf region for more than 120 days, there were increased frequencies of skin rashes and unintentional weight loss. In the follow-up survey, there was a higher frequency of skin rashes among the veterans deployed for less than 120 days, but the frequency was no longer elevated in the veterans deployed for more than 120 days. Additional findings in the follow-up survey were an increased frequency of cough in both groups of deployed veterans, self-reported memory problems in veterans deployed for less than 120 days, and headaches, lumps or cysts in the breast, and abnormal Pap smear in the combined group of deployed veterans. An increased incidence of post-traumatic stress disorder (assessed using the Mississippi scale for combat-related post-traumatic stress disorder) was observed in both groups of deployed veterans 2 years after the war.

[Canadian Department of National Defence. 1998. Health Study of Canadian Forces Personnel Involved in the 1991 Conflict in the Persian Gulf. Volumes I and II. Prepared for the Gulf War Illness Advisory Committee, Department of National Defence, by Goss Gilroy Inc. Management Consultants, Ottawa. April 20, 1998.  
[http://www.DND.ca/menu/press/reports/health/health\\_study\\_e\\_voll\\_TOC.htm](http://www.DND.ca/menu/press/reports/health/health_study_e_voll_TOC.htm). ]

A health survey questionnaire was mailed to 9947 Canadian Forces personnel, including all Canadian Gulf War veterans and a sample of Canadian Forces who served elsewhere during the Gulf War. Completed questionnaires were returned by 3113 deployed (73%) and 3439 non-deployed (60.3%) veterans. Responses between the two groups were statistically compared using logistic regression analysis to adjust for potential confounders such as age, gender and military rank. Deployed and non-deployed groups were reported to have similar socio-demographic characteristics. Gulf-deployed veterans, compared with non-deployed veterans, reported higher prevalences of symptoms of chronic fatigue, cognitive dysfunction, multiple chemical sensitivity, major depression, post-traumatic stress disorder, anxiety, fibromyalgia and respiratory diseases (bronchitis and asthma together), as well as higher numbers of children with birth defects (before, during, and after the Gulf War).

### ***Neurophysiological and Neuropsychological Evaluations of Symptomatic Gulf War Veterans***

[Axelrod, B.N. and I.B. Milner. 1997. Neuropsychological findings in a sample of Operation Desert Storm veterans. *J. Neuropsychiatry*. 9: 23-28.]

Axelrod and Milner (1997) examined neuropsychological performance, performance on the Minnesota Multiphasic Personality Inventory (MMPI), and subjective complaints of cognitive deficiency in a self-selected group of 44 male Gulf War veterans who were members of a National Guard reserve unit that contained 78 male veterans. Neuropsychological performance was evaluated using several measures in the general areas of intellectual functioning, achievement and language, learning and memory, and executive and motor functioning. For the group of veterans, means and standard deviations for neuropsychological measures and MMPI test scores were not

compared with measures in a matched control group but rather to clinically-accepted normal values. The study authors did not discuss the validity of the normal values or the characteristics of the populations from which they were derived. In the veterans, deficits in neuropsychological measures ( $p < 0.005$ ), relative to normal values, were observed only in finger dexterity in two of six measures of motor functioning (grooved pegboard - dominant and non-dominant) and in the Stroop color and word test, which represents three of the twelve measures of executive functioning. On the MMPI test, the only scale that exceeded a “cutoff” value of 70 in the veterans was body complaints, which is associated with reports of fatigue, concern about physical health, and specific complaints such as shortness of breath, dizzy spells, and diarrhea. Veterans with lower finger dexterity (grooved pegboard) scores ( $n = 15$ ), when compared with the remainder of the group ( $n = 29$ ), had lower neuropsychological performance in measures of intellectual functioning (3 of 4 measures), achievement and language (1 of 5), executive functioning (5 of 12), and motor functioning (3 of 6, including the finger dexterity deficit) and had higher scores on several clinical and supplemental scales of the MMPI, but did not differ with regard to self-reported medical symptoms or cognitive difficulties. Veterans with impaired color-word performance ( $n = 12$ ), when compared with the remainder of the group ( $n = 32$ ), had lower neuropsychological performance in measures of intellectual functioning (3 of 4 measures), achievement and language (2 of 5), learning and memory (2 of 9), executive functioning (10 of 12, including the color-word performance deficit), and motor functioning (4 of 6), had higher scores on several clinical and supplemental scales of the MMPI. The group with impaired color-word performance also reported a significantly higher report of recurring diarrhea but did not differ with regard to self-reported cognitive difficulties. Veterans with self-reported complaints of cognitive difficulties ( $n = 17$ ), when compared with those who denied any subjective neuropsychological changes ( $n = 27$ ), had lower neuropsychological performance only in measures of executive functioning but had higher scores on several clinical and supplemental scales of the MMPI (depression, organic symptoms, family problems, autism, religious fundamentalism, manifest hostility, psychoticism, suspicion, depression, resentment, tension). In summary, this group of 44 Gulf War veterans showed only minor deficits in neuropsychological performance compared with clinically-accepted normal values but had elevated psychological distress as indicated by higher scores on the MMPI. However, the findings in this study cannot definitively be extended to other Gulf War veterans or linked to service in the Gulf War because the study group was small and self-selected, no pre-deployment studies were performed on these veterans, and similar studies were not performed in a matched control group of veterans of the same era who were not deployed in the Gulf War.

[Amato, A.A., A. McVey, C. Cha, E.C. Matthews, C.E. Jackson, R. Kleingunther, L. Worley, E. Cornman, K. Kangan-Hallet. 1997. Evaluation of neuromuscular symptoms in veterans of the Persian Gulf war. *Neurology*. 4-12.]

Amato et al. (1997) performed neuromuscular studies in 20 Gulf War veterans who complained of severe muscle fatigue, weakness, or myalgias of 6 months duration or longer that interfered with their activities of daily living. Symptoms began 1 month to 3.5 years after returning home from the Gulf War and were present for 6 months to 3.5 years at the time of their neuromuscular



evaluation. The group of fifteen men and five women, ages 24 to 50 years, had been referred for comprehensive evaluation by specialists in neuromuscular disease from a group of 263 patients that had been evaluated by specialists in neurology, psychiatry, neuropsychology, infectious disease, and general internal medicine. The neuromuscular studies, performed by staff from the Departments of Neurology and Internal Medicine at the Wilford Hall Medical Center, San Antonio, Texas and the Departments of Medicine/Neurology and Pathology/Neuropathology at the University of Texas Health Science Center at San Antonio, included serum creatine kinase, erythrocyte sedimentation rate, thyroid function tests, graded manual muscle strength of 36 muscle groups, exercise forearm tests, nerve conduction studies, a repetitive nerve stimulation study, quantitative and single-fiber electromyography (EMG), and histologic evaluation of muscle biopsy tissues by 11 routine histologic and enzymatic stains. General physical and neurologic examinations were unremarkable, with no evidence of polyneuropathy. Six patients, five of whom were muscular males, had mildly elevated serum creatine kinase levels. Nerve conduction study results were normal except in two patients with carpal tunnel syndrome. EMG findings were normal except for one patient who had mildly-increased jitter on single-fiber EMG and also had elevated serum creatine kinase and tubular aggregates on muscle biopsy. Five patients had non-specific histologic abnormalities noted at muscle biopsy, but these histologic findings were not sufficient to diagnose an inflammatory myopathy. Electroencephalograms were normal in all patients and head CT scans and neuropsychiatric tests, performed on patients complaining of headaches, memory loss, or difficulty with concentration were also normal. Ten of the twenty patients had signs of depression or an anxiety disorder upon evaluation by psychiatry consultants. Three patients were diagnosed with somatoform disorders. One patient had atasia-abasia and documented pseudoseizures. Rheumatologists did not diagnose autoimmune or connective tissue disorders, and infectious disease consultants found no diseases. In summary, extensive neuromuscular and related studies showed no clear evidence of neuromuscular pathology in the majority of 20 Gulf War Veterans who had been referred for comprehensive evaluation by specialists in neuromuscular disease because of subjective complaints of severe weakness or myalgias that limited activities of daily living. This study is limited by the small size of the study group and the apparent absence of blinded evaluation.

[Haley, R.W., T.L. Kurt, J. Horn. 1997a. Is there a Gulf War Syndrome? Searching for syndromes by factor analysis of symptoms. *JAMA*. 277: 215-222; Haley, R.W., J. Horn, P.S. Roland, W.W. Bryan, et al. 1997b. Evaluation of neurologic function in Gulf War veterans. A blinded case-control study. *JAMA*. 277: 223-230; Haley, R.W. and T.L. Kurt. 1997. Self-reported exposure to neurotoxic chemical combinations in the Gulf War. *JAMA*. 277: 231-237.]

In a series of three studies, a group of 249 U.S. Gulf War veterans answered questions about health symptoms and wartime exposures and questions from a standardized psychological personality assessment questionnaire (Haley et al., 1997a,b; Haley and Kurt, 1997). The 249 respondents were part of 606 Gulf War veterans of the 24<sup>th</sup> Reserve Naval Mobile Construction Battalion living in five southeast states. Serious health problems were reported by 175 of the respondents.

In the first study (Haley et al., 1997a), principal factor analysis of the reported symptoms identified six possible syndromes of suspected neurologic injury and identified the syndromes in 63 subjects. The three syndromes with the strongest associations (the other three syndromes were reported to display only weak associations among symptoms) were given the following names: *impaired cognition* (associated with: attention, memory, and reasoning problems; insomnia; depression; daytime sleepiness; and headaches), *confusion-ataxia* (associated with thinking problems; disorientation; balance disturbances; vertigo; and impotence), and *arthro-myoneuropathy* (associated with: joint and muscle pain; muscle fatigue; difficulty lifting; and extremity paresthesias).

In the second study, Haley (1997b) used the syndrome definitions to compare results in batteries of neuropsychological, neurological, clinical, and blood tests between cases and controls. “Cases” were defined as the subjects with the five highest symptom scores among those with *impaired cognition* and those with *arthro-myoneuropathy* (i.e., 5 cases from each group), and the subjects with the 13 highest symptom scores among those diagnosed with *confusion-ataxia*. The 20 controls were matched for age, sex, and educational level to cases in the *confusion-ataxia* syndrome, and the administrators of the tests were blinded as to group identity of the subjects. Haley et al. (1997b) noted that the *confusion-ataxia* syndrome was oversampled because this syndrome appeared to be more disabling than the other two syndromes. Motor and reflex functions were evaluated clinically. Neurological examinations included: tests of auditory and vestibular function, brain stem auditory evoked potentials, somatosensory and visual evoked potentials, and brain imaging (magnetic resonance imaging and single-photon emission computed tomography). The Halstead-Reitan test battery evaluated neuropsychological endpoints. Blood tests included complete hematology and numerous biochemical variables including activities of creatinine kinase, butyryl cholinesterase and red blood cell cholinesterase, and acetylcholine receptor antibody level.

The frequency of abnormalities in the various blood tests or in the brain images were not significantly different between cases and controls (Haley et al., 1997b). Clinical neurological examinations found no statistically significant differences between the cases and controls, except that 6/22 cases showed weakness of the lower extremities (one case was excluded from the analysis because of conscious efforts “to embellish the examination”), compared with 1/20 in the control group. Based on neuropsychological test results, mean scores on the Halstead Impairment Index and the General Neuropsychological Deficit Scale were statistically significantly greater in cases than in controls, indicating greater neuropsychological dysfunction. In auditory and vestibular function tests, the frequency of cases with abnormal ocular motility was not significantly different from controls, but significantly more controls (4/23) showed abnormal spontaneous nystagmus (rhythmic movement of eyeball) than cases (0/20). Cases, statistically compared with controls, showed significantly diminished velocity of nystagmus in response to stimulation of the ear by heat or cold and significantly increased interocular asymmetry of saccadic velocity and of nystagmus in response to rotation. The frequencies of subjects with abnormal values of somatosensory-evoked-potential variables or brain stem auditory-evoked-potential variables were not significantly different between cases and controls, but statistically

significant differences were found between cases and controls for mean values for several of the variables (e.g., greater interside asymmetry of the wave I to wave II interpeak latency of brain stem auditory evoked potentials, and increased latency of the lumbar-to-cerebral peaks on posterior tibial somatosensory evoked potentials). The clinical significance of the differences observed between cases and controls is uncertain. Six neurologists, who were blinded to the identity of the subjects, reviewed the findings on each individual and concluded that “the clinical and laboratory findings were nonspecific and not sufficient to diagnose any known syndrome in any subgroup of the subjects.” Nevertheless, Haley et al. (1997b) speculated that the observed statistically significant differences between cases and controls in several objective measures of neurophysiological and audiovestibular variables may have a relationship with “sublethal exposures to cholinesterase-inhibiting chemicals”, and noted that additional research is necessary, including examining the same, and additional, endpoints (e.g., neuromuscular and nerve conduction velocity variables) in a greater number of subjects (cases and controls).

In the third study, Haley and Kurt (1997) used self-reported exposure information (e.g., exposure to pesticides, chemical weapons, smoke from oil well fires, and pyridostigmine bromide) from the 249 Gulf War veterans to look for statistical associations between exposure to risk factors and the occurrence of the three “factor analysis-derived syndromes” described earlier. Statistically significantly increased relative risks (RR) were reported for the:

- C *impaired cognition* syndrome in those who reported wearing pet flea-and-tick collars [RR = 8.2 (95% CI = 2.9-23.5)] and those whose main job involved security [RR = 6.4 (2.1-19.30)];
- C *confusion-ataxia* syndrome in those reporting experiencing a likely chemical weapons attack [RR = 7.8 (2.3-25.9)], those located in sector 7 in northeastern Saudi Arabia on January 20, 1991 [RR = 4.3 (1.9-10)], and those reporting severe advanced adverse effects from pyridostigmine bromide [RR = 32.4 (7.8-135)];
- C *arthro-myo-neuropathy* syndrome in those reporting typically applying a relatively large amount of insect repellent to the skin [RR = 7.8 (2.4-24.7)] and those reporting severe advanced effects from pyridostigmine bromide [RR = 3.9 (1.3-12.1)].

Haley and Kurt (1997) concluded that the findings provide support for the hypothesis that the three factor analysis-derived syndromes may represent variants of organophosphate-induced delayed neuropathy due to exposure to mixtures of anti-cholinesterase agents (pesticides, insect repellent, and pyridostigmine), acknowledging the limitation of the self-reported nature of the exposure determinations.

### ***Mycoplasma and Bacterial Infections in Gulf War Veterans with Illnesses: Detection and Treatment***

[Nicolson G.L., N.L. Rosenberg-Nicolson. 1995. Doxycycline treatment and desert storm. J. Amer. Med. Assoc. 273:618-619.]

Prior to conducting studies on detection of mycoplasma in Gulf War veterans, Nicolson and Rosenberg-Nicolson (1995) suggested that many of the health complaints of Gulf War veterans listed by the report of the NIH Technology Assessment Workshop Panel (1994a,b) might be associated with aggressive pathogenic mycoplasma infections such as *Mycoplasma incognitus* or *Mycoplasma penetrans*, and that such infections should be treatable with multiple courses of antibiotics such as doxycycline or macrolides. Nicolson and Rosenberg-Nicolson (1995) also reported that they conducted a phone/letter survey of 73 Gulf War veterans who had the symptoms listed by the NIH Technology Assessment Workshop Panel (1994) and that 55 of the 73 indicated that “they had good responses with doxycycline and eventually returned to normal duty.” No firm conclusions can be drawn from this uncontrolled survey study because no additional information was reported to characterize these patients, the antibiotic treatment regimen they received or what constituted a good response. In addition, the subjective reports of good responses cannot clearly be linked to suppression of mycoplasma infection, since doxycycline would be expected to be effective against other unrecognized organisms.

[Nicolson, G.L. and N.L. Nicolson. 1996. Diagnosis and treatment of mycoplasmal infections in Persian Gulf War illnesses - CFIDS patients. *Intl. J. Occup. Med. Immunol. Toxicol.* 5: 69-78.]

Nicolson and Nicolson (1996) used a Gene Tracking technique to assess the presence of mycoplasma gene sequences in the nuclei of leukocytes isolated from blood samples from 30 Gulf War veterans with symptoms of Gulf War illness or symptomatic members of their families (collectively referred to as Gulf War illness patients) and from 21 “normal controls”. No objective data were provided to characterize the medical histories or general medical condition of the test subjects at the time of the study. Mycoplasma gene sequences were detected in 14/30 Gulf War illness patients but were not detected in the normal controls. Using probes for *Mycoplasma fermenting* (incognitus strain), *M. genitalium*, *A. laidwairi*, and other mycoplasmas, 9/14 mycoplasma-positive patients were found to have gene sequences only for *Mycoplasma fermenting* (incognitus strain). Treatment suggestions for each of the 14 mycoplasma-positive patients were made to primary care physicians. Eleven of the 14 mycoplasma-positive patients were reported to have completely recovered after multiple cycles of treatment with doxycycline or ciprofloxacin antibiotics. Case reports of the symptoms, course of treatment, and outcome were presented for 11/14 treated patients. Upon retesting of four of the patients who were reported to have completely recovered after antibiotic therapy, no evidence of mycoplasma gene sequences was found in their blood leukocytes.

[Nicolson, G.L., N.L. Nicolson, M. Nasralla. 1998. Mycoplasmal infections and fibromyalgia/chronic fatigue illness (Gulf War Illness) associated with deployment to Operations Desert Storm. *Int. J. Med.* 1:80-92; Baseman, J.B. and J.G. Tully. 1997. Mycoplasmas: Sophisticated, reemerging, and burdened by their notoriety. *Emerging Infect. Dis.* 3: 21-32.]

In a study similar to that of Nicolson and Nicolson (1996), Nicolson et al. (1998), using the Gene Tracking method to assess the presence of mycoplasma gene sequences in the nuclei of leukocytes isolated from blood samples, found evidence of mycoplasma gene sequences in 76/170 Gulf War

veterans and symptomatic members of their families who had signs and symptoms of Gulf War illness/fibromyalgia/chronic fatigue syndrome and in 2/41 members of a control group of “nondeployed, healthy adults”. It was not indicated whether or not the control group consisted of veterans of the Gulf War era who had not been deployed in the Gulf War. It was also not clear if the results for the group of 170 included results from a group of 30 Gulf War veterans and symptomatic family members that were reported previously by Nicolson and Nicolson (1996). Nicolson et al. (1998) also reported the presence of mycoplasma gene sequences in 2/2 British veterans with symptoms of Gulf War illness/ chronic fatigue syndrome but did not comment further on these subjects. Gene sequences characteristic of *Mycoplasma fermenting* were reported to have occurred in “about 2/3” of the Gulf War illness patients. Treatment of 73 of the mycoplasma-positive patients with multiple cycles of doxycycline, ciprofloxacin, or azithromycin was reported to result in recovery in 58 patients after two to six treatment cycles. Criteria for recovery were not presented. Case reports of the symptoms, course of treatment, and outcome were presented for seven of the patients who received antibiotics. Upon retesting of 19 of the patients who were reported to have recovered after antibiotic therapy, no evidence of mycoplasma gene sequences was found in their blood leukocytes.

General limitations of the studies by Nicolson and colleagues include:

- C Blind testing of specimens from Gulf War veterans was not performed and appropriate control groups were not studied to determine whether or not infection with mycoplasma is associated with either illness or participation in the Gulf War. The inclusion of healthy referent groups seems important since mycoplasma species appear to comprise normal microbial flora of healthy persons (Baseman and Tully, 1997).
- C The sensitivity and reproducibility of the Gene Tracking method for detection of mycoplasma gene sequences in human leukocytes was not defined.
- C Diagnostic criteria were not defined to characterize a patient as “recovered”, “fully recovered” or in a state of “relapse” during or following antibiotic therapy.
- C A possible placebo effect has not been investigated.

## Appendix D. Ongoing Research Related to Illnesses Among Gulf War Veterans

### Sources:

RWG (Research Working Group). 1998. Annual Report to Congress: Federally Sponsored Research on Gulf War Veterans' Illnesses for 1997. March, 1998. Persian Gulf Veterans Coordinating Board.

RWG (Research Working Group). 1999. Interagency Gulf War Research Projects Database. January, 1999. Persian Gulf Veterans Coordinating Board.

This Appendix contains short descriptions of ongoing, U.S. Government-funded research projects grouped according to the following topics:

- A. Multiple Chemical Sensitivity in Gulf War Veterans
- B. Genetic Differences in Susceptibility / Biomarkers of Disease
- C. Toxicity of Mixtures of Chemicals and Other Risk Factors
- D. Treatment of Gulf War Veterans with Illnesses
- E. Toxicity of Low-Level Exposure to Chemical Warfare Agents
- F. Toxicity of Pyridostigmine Bromide
- G. Assessment / Definition of Gulf War Illnesses
- H. Disease Prevalence and Associations between Chemical Exposures and Illnesses in Gulf War Veterans
- I. Toxicity from Depleted Uranium.

For each project the sponsoring agency (DoD, DVA, DHHS) and research project number are noted (e.g., DoD-1; DVA-1 or DHHS-1)).

### A. Multiple Chemical Sensitivity in Gulf War Veterans

*Georgetown University and VA Medical Center, Washington, DC: D. Clauw, M.D. DoD-31. (Also cited in section G.)*

Measure and compare physiologic variables (e.g., pain sensitivity, esophageal smooth muscle motility) and biochemical variables (changes in neurohormone levels in response to different stressors, cerebral fluid levels of neurotransmitters) in Gulf War veterans with unexplained chronic symptoms, in civilian patients with chronic fatigue syndrome, chemical sensitivities, or fibromyalgia, and in healthy controls.

*Veterans' Administration Medical Center, Boston, Massachusetts. R. White, Ph.D. Neuropsychological Functioning in Persian Gulf Era Veterans. DoD-32. (Also cited in section G.)*

Compare results from in-depth neuropsychological evaluations in treatment-seeking Gulf War veterans, non-deployed veterans of Gulf War era, and groups of healthy (non-treatment seeking) veterans. Development and administration of a questionnaire to identify multiple chemical sensitivity.

*Veterans' Administration Medical Center, Boston, Massachusetts: J. Wolfe. Female Gender and Other Potential Predictors of Functional Health Status Among Persian Gulf War Veterans. DoD-52. (Also cited in section G.)*

Identification and description of self-reported Gulf War environmental and psycho-social combat-theater exposures, functional health status, and health perceptions in a cohort of male and female Gulf War veterans. Development of a survey to identify subjects with multiple chemical sensitivity (MCS)-like symptoms and examination of potential correlations between specific risk factors and MCS-like symptoms.

*University of Medicine and Dentistry of New Jersey - Robert Wood Johnson Medical School: H. Kipen, M.D., M.P.H. Defining Gulf War Illness. Cooperative Research Agreement with CDC. DHHS-6. (Also cited in section G.)*

Evaluate the persistence and stability of self-reported symptoms in two samples of U.S. Gulf War veterans. Compare the appropriateness of standard working definitions for chronic fatigue syndrome, fibromyalgia, multiple chemical sensitivity with factor-analysis-derived case definitions to describe unexplained illnesses in Gulf War veterans.

*Veterans Administration Medical Center, East Orange, NJ: B. Natelson, M.D. Physiological and Psychological Assessments of Persian Gulf Veterans. DVA-5B. (Also cited in section G.)*

Compare physiological, immunological, and neuropsychological variables in healthy veterans, veterans with chronic fatigue syndrome and/or chemical sensitivities, and civilians with chronic fatigue syndrome or chemical sensitivities.

*Veterans' Administration Medical Center, East Orange, New Jersey: N. Fiedler, Ph.D. Effects of Exertion and Chemical Stress on Persian Gulf Veterans. DVA-5C. (Also cited in section G.)*

Examination of effects of acute exhaustive exercise or acute exposure to 5 ppm diesel fumes on psychophysiological variables (e.g., heart rate, blood pressure, respiration rate) and performance in a vigilance task in groups of healthy Gulf War veterans and groups of Gulf War veterans previously diagnosed with fatiguing illness (chronic fatigue syndrome and/or chemical sensitivities).

*Veterans' Administration Medical Center, Tuscon, Arizona: I.R. Bell, M.D., Ph.D. Cross-Sensitization as a CNS Model for Gulf War Chemical Intolerance. DVA-48. (Also cited in section G.)*

Comparison of blood pressure, heart rate, and neurobehavioral responses to repeated laboratory exposures to placebo, jet fuel, or perfume in three groups of Gulf War veterans: 1) ill with increased chemical intolerance attributed to military service; 2) ill without increased chemical intolerance; and 3) healthy without chemical intolerance; and a group of healthy Gulf War-era non-deployed veterans. Measure and compare characteristics associated with enhanced vulnerability to sensitization among these groups.

## **B. Genetic Differences in Susceptibility / Biomarkers of Disease**

*University of North Carolina, Chapel Hill: D.H. Overstreet, Ph.D. Effects of Pyridostigmine in Flinders line Rats Differing in Cholinergic Sensitivity. DoD-33. (Also cited in section F.)*

Examine physiologic and biochemical responses to pyridostigmine in a genetic line of rats with putative supersensitivity to organophosphate nerve agents. Examine if repeated exposure to pyridostigmine protects against short-term body temperature decreases induced by organophosphate cholinergic agents (diisopropylphosphate, chlorpyrifos).

*Hebrew University of Jerusalem, Israel: H. Soreq, Ph.D. Transgenic Engineering of Cholinesterases: Tools for Exploring Cholinergic Responses. DoD-51.*

Examination of the protective value and potential side-effects of transgenic expression of various cholinesterases in mice. Transgenic mice with two copies of the human gene encoding the synaptic form of acetylcholinesterase show elevated activity levels of acetylcholinesterase in central nervous system cholinergic neurons, less sensitivity to organophosphate neurotoxicity, and deficits in cognitive functions such as learning and memory. Other transgenic lines of mice will be developed with different genes encoding acetylcholinesterases with different subcellular and tissue-specific patterns of expression. Sensitivity to organophosphate neurotoxicity and cognitive and neuromotor behavior will be evaluated in these mice. DNA from human subjects who display hypersensitivity to anti-cholinesterase agents, such as pyridostigmine, organophosphate insecticides, and organophosphate warfare nerve agents, will be examined in search of particular gene sequences that may correlate with hypersensitivity.

*University of Nebraska Medical Center: O. Lockridge, Ph.D. Butyrylcholinesterase Genetic Variants in Persons with Gulf War Illness. DoD-60.*

Comparison of blood butyrylcholinesterase activity levels and genotype in healthy and ill Gulf War veterans.

*Veterans' Administration Medical Center, Boston, Massachusetts: D. Sherr, Ph.D. The Aromatic Hydrocarbon Receptor (AhR) as a Biomarker of Susceptibility. DVA-4C.*

Examination of PAH-induced effects on immunological and cell transformation variables in transgenic mice with varying levels of AhR expression in lymphocytes. Results will test hypothesis that levels of AhR in mice correlate with the intensity of immunotoxic and carcinogenic responses to PAHs. Comparison of levels of AhR in peripheral blood lymphocytes in symptomatic and asymptomatic Gulf War veterans will examine possible association between putative PAH sensitivity and Gulf War Illnesses.

*Veterans' Administration Medical Center, East Orange, New Jersey: J. Ottenweller, Ph.D. Effects of Genetics and Stress on Neurobehavioral Responses to Pyridostigmine in Rats. DVA-5D. (Also cited in section F.)*

Examination of neurobehavioral variables (e.g., startle response and behavioral rhythms) in two strains of rats at varying times after exposure to pyridostigmine bromide for 7 days and a 3-day chronic stress regime.

*Veterans' Administration Medical Center, East Orange, New Jersey: R.J. Servatius, Ph.D. Sensitivity to Pyridostigmine Bromide: Persistent Neural Dysfunction. DVA-49. (Also cited in section B.)*

Determination of pharmacokinetics of pyridostigmine bromide in two genetic strains of rats that differ in inherent levels of butyrylcholinesterase. Comparison of the effects of pyridostigmine bromide and the cholinesterase inhibitors edrophonium and neostigmine on butyrylcholinesterase activity and startle response. Examine the effects of physically-induced stress and pyridostigmine pretreatment on brain acetylcholinesterase activities.

### **C. Toxicity of Mixtures of Chemicals and Other Risk Factors**

*University of Florida: F. van Haaren, Ph.D. Neurobehavioral and Immunological Toxicity of Pyridostigmine, Permethrin, and DEET in Male and Female Rats. DOD- 37.*

Evaluate effects of exposure rats to pyridostigmine bromide, permethrin, and DEET, alone or in combination, on several measures of neurobehavior and immune system function.

*Battelle Memorial Institute, Columbus, Ohio: C.T. Olson, Ph.D. Assessment of Subchronic Neurobehavioral and Neuropathic Effects in Rats. DOD-54.*

Examination of neurobehavioral and neuropathological measures in rats 30 days after exposure for 4 days to low levels of chemicals, alone or in combination of chemicals, to which Gulf War troops may have been exposed (sarin, pyridostigmine bromide, DEET).

*Prinz Maurits Laboratory, Netherlands: H. vanHelden, Ph.D. Low-level Exposure of Guinea Pigs and Marmosets to Sarin Vapor in Air: Diagnosis/Dosimetry, Lowest Observable Effect Levels, Performance-Incapacitation, and Possible Delayed Effects. DOD-55. (Also cited in section E.)*

Examination of respiration variables, central nervous system variables, and miosis in guinea pigs and marmosets acutely exposed by inhalation to low levels of airborne sarin (with and without pretreatment with pyridostigmine). Examinations for delayed effects following acute exposure will be conducted.

*University of California: B. Wilson, Ph.D. Low-Level Sarin Neurotoxicity and Its Modulation by Pyridostigmine. DoD-56. (Also cited in section E.)*

Morphological and biochemical examinations of brain, spinal cord, and peripheral neuromuscular and sensory systems in mice and hens acutely exposed to low levels of airborne sarin (with or without pre- or co-exposure with pyridostigmine). Examinations for delayed effects following acute exposure will be conducted.



*Battelle Memorial Institute, Columbus, Ohio: C.T. Olson, Ph.D. Neurophysiologic and Neuropathologic Effects in Monkeys Exposed to Low Levels of Sarin, Pyridostigmine, Pesticides, and Botulinum Toxoid. DOD-61.*

Examination of neurophysiological variables, blood biochemical variables (e.g., acetyl cholinesterase and neurotoxic esterase), and histopathology of tissues in groups of monkeys given 14-day exposures to the following substances or mixtures of substances at dose levels that produce cholinesterase inhibition without observable signs of intoxication: saline control; positive control - diisopropyl fluorophosphate; sarin + botulinum toxoid; pyridostigmine + DEET + chlorpyrifos; and (sarin + botulinum toxoid) + (pyridostigmine + DEET + chlorpyrifos). Neurophysiologic variables will be examined immediately after exposure and at 60, 90, and 180 days after exposure.

*Southern Illinois University: S.M. Somani, Ph.D. Sarin and Pyridostigmine Interaction under Physical Stress: Neurotoxic Effects in Mice. DoD-62.*

Examination of the interactive neurotoxic effects of low-level sarin exposure, physical exercise, and pyridostigmine exposure on neurobehavioral, electrophysiological, and biochemical variables and on microscopic structure of nervous system tissues in mice.

*Virginia Polytechnic Institute: S. Holladay, Ph.D. Immunotoxicity of Dermal Permethrin and Cis-Urocanic Acid. DHHS -7*

Examine immunological variables in mice after dermal exposure to the insecticide permethrin, alone and in combination with cis-urocanic acid.

*Lawrence Livermore National Laboratory: J.S. Vogel, Ph.D. Strategy to Identify Non-Additive Response to Chemical Mixtures. DHHS-8.*

Measure quantities of an organophosphate insecticide in nerve cell membranes in mice following low-levels of exposure to the insecticide alone and in combination with low-levels of mixtures of other ester compounds.

*Duke University Medical Center: M. Abou Donia, Ph.D. Long-term Effects of Subchronic Exposure to Sarin, Alone and with Stress or Other Chemicals. DoD-72.*

Examination of neurobehavioral variables, permeability of the blood-brain barrier, and electrophysiological variables in rats exposed subchronically to low levels of sarin alone and in combinations with stress, heat, or pyridostigmine. Other exposure regimes will examine variables in response to: low-level sarin plus heat and pyridostigmine; sarin plus stress and pyridostigmine; and sarin plus stress, heat, pyridostigmine, DEET, and permethrin.

*Duke University Medical Center: M. Abou Donia, Ph.D. Toxic Interactions of Prophylactic Drugs and Pesticides. DoD-75.*

Examination of neurobehavioral variables, cholinesterase activities in blood, brain, and liver, and permeability of the blood-brain barrier in rats exposed for 60 days to pyridostigmine bromide, DEET, and permethrin, alone, in binary and tertiary combinations, and at various dose levels.

*Medical University of South Carolina: D.E. Keil, Ph.D. Evaluation of Immunotoxicity Due to Concurrent Exposure to DEET, Pyridostigmine, and JP-8 Jet Fuel. DoD-76*

Examine immunological variables (e.g., natural killer cell activity, macrophage function, disease resistance) in animals (species not specified) exposed to sub-chronic, low levels of DEET, pyridostigmine bromide and JP-8 jet fuel. Hypothesis to test is that exposure to these 3 agents acting together leads to immune system dysfunction.

*North Carolina State University: J. Riviere, Ph.D. Percutaneous Absorption of Chemical Mixtures Relevant to the Gulf War. DoD-77.*

Examine dermal absorption and skin toxicity of pyridostigmine bromide, permethrin, and DEET, alone and together, using a flow through diffusion technique with porcine skin or an isolated perfused porcine skin flap technique.

*New York University Medical Center: H.L. Evans. Experimental Models of Gulf War Syndrome. DoD-78.*  
Measurement of cognitive function variables, sensory evoked potential variables, diurnal rhythms in locomotion, and pulmonary function variables in rats and macaques before and after low-level exposures to (alone and in combination): inhaled sarin or soman; orally administered pyridostigmine; and psychological stress from exposure to novel stimuli.

#### **D. Treatment of Gulf War Veterans with Illnesses**

*Louisiana Medical Foundation: E. Hyman, M.D. Antibacterial Treatment Method Based on the Excretion of Dead and Decaying Spherical Bacteria. DoD-67.*

Clinical evaluation for bacteriuria in Gulf War veterans with “Desert Storm Syndrome” and effectiveness of antibiotic treatment or placebo in relieving symptoms of fatigue, cognitive dysfunction, joint and somatic pain, headache, dermatitis, and gastrointestinal dysfunction.

*Multiple VA Medical Centers: S. Donta, M.D. DVA/DoD Multi-site Treatment Trial for Chronic Fatigue Syndrome and Fibromyalgia in Gulf War Veterans. VA/DoD-1D & IV.*

A 2-year, multiple-site, randomized control trial (starting in 1999 and ending in 2001) to compare treatment methods for U.S. Gulf War veterans who have unexplained chronic symptoms of pain, fatigue, and/or cognitive difficulties. Patients will be Gulf War veterans who are chronically experiencing at least two of the following self-reported symptoms: 1) fatigue that limits work, recreational, or social activity; 2) musculoskeletal pain in two or more body regions; and 3) difficulties in memory, concentration, or attention. The program will evaluate 339 randomly assigned patients in each of four treatment groups: 1) “usual and customary care” (the control group); 2) cognitive behavioral therapy plus usual and customary care; 3) aerobic exercise plus usual and customary care; and 4) cognitive behavioral therapy, plus aerobic exercise, and usual and customary care. Treatment will be in a group format and will last for 3 months (one hourly session per week for 12 weeks).

*Walter Reed Army Institute of Research: J. Meyerhoff. Combat Stress Pharmacotherapy. DoD 6A.*

Testing of behaviorally-active clinically-available drugs (e.g., valium, beta blockers, antidepressants) to reverse or prevent conditioned-defeat behavior in mice. The investigators are using the conditioned-defeat behavior in mice as a model of combat stress reaction and post-traumatic stress disorder.

*Veterans’ Administration Medical Center, Perry Point & Multiple Sites: S. Donta, M.D. Antibiotic Treatment of Gulf War Veterans’ Illnesses. DVA-55*

This is a 30-month, prospective, randomized, double-blind, placebo-controlled clinical trial. The trial will identify 450 Gulf War veterans who are experiencing at least two of three chronic symptoms (fatigue, musculoskeletal pain, and neurocognitive dysfunction) and who are mycoplasma-positive. Subjects will be randomly assigned to 12-month treatments with either 300 mg doxycycline per day or placebo. Patients will be seen monthly during the medication phase and at 18 months. Physical function will be evaluated before treatment starts, and at 3, 6, 9, 12 and 18 months. Patients will also complete questionnaires designed to provide measures of pain, fatigue, and neurocognitive dysfunction.

#### **E. Toxicity of Low-Level Exposure to Chemical Warfare Agents**

*TNO Prinz Maruits Laboratory, Rijswijk, Netherlands: H.P. Benschop, Ph.D. Toxicokinetics of VX in Rats, Hairless Guinea Pigs and Marmosets. DoD-50.*

Develop methodology for and clarify the toxicokinetics of VX stereoisomers in laboratory animals.

*Lovelace Inhalation Toxicology Research Institute, Albuquerque, New Mexico: R. Henderson, Ph.D. Long-term Effects of Subclinical Exposures to Sarin in Rats.. DoD-53.*

Examination of toxicokinetics of sarin in nervous tissue of rats exposed, once or repeatedly, by inhalation to low and high airborne concentrations. Examine brain biochemical markers of effect (e.g., muscarinic and nicotinic

receptor densities, acetylcholinesterase activities) immediately following exposure and one month after exposure, to examine persistence of effects.

*Prinz Maurits Laboratory, Netherlands: H. vanHelden, Ph.D. Low-level Exposure of Guinea Pigs and Marmosets to Sarin Vapor in Air: Diagnosis/Dosimetry, Lowest Observable Effect Levels, Performance-Incapacitation, and Possible Delayed Effects. DoD-55. (Also cited in section C.)*

Examination of respiration variables, central nervous system variables, and miosis in guinea pigs and marmosets acutely exposed by inhalation to low levels of airborne sarin (with and without pretreatment with pyridostigmine). Examinations for delayed effects following acute exposure will be conducted.

*University of California: B. Wilson, Ph.D. Low-Level Sarin Neurotoxicity and Its Modulation by Pyridostigmine. DoD-56. ( Also cited in section C.)*

Morphological and biochemical examinations of brain, spinal cord, and peripheral neuromuscular and sensory systems in mice and hens acutely exposed to low levels of airborne sarin (with or without pre- or co-exposure with pyridostigmine). Examinations for delayed effects following acute exposure will be conducted.

*University of Oregon Health Sciences: P. Spencer, Ph.D. Persian Gulf Veterans: Epidemiological and Clinical Evidence for Residual Organophosphate Neurotoxicity. DoD-63. (Also cited in section H.)*

Health survey and clinical examination of neuropsychological and neurophysiological variables in a sample of the 20,000 U.S. troops who were located within a 50-km radius of Khamisiyah during the first two weeks of March 1991. Comparison groups will include subjects from other Desert Storm troops, subjects from other Desert Shield troops, subjects from other U.S. military groups that served during, but not in, the Persian Gulf, and civilians with a documented history of exposure to organophosphate insecticides that produced non-convulsive health symptoms.

*Institute of Medicine/ Medical Follow-up Agency: P. Renzullo. Five-year Follow-up of Army Personnel Exposed to Chemical Warfare Agents. DoD-69. (Also cited in section H.)*

Compare hospitalization rates and mortality rates during a 5-year, post-Gulf War period among the following groups: 1) subjects from 2 U.S. Army engineer battalions involved with the March 1991 destruction of the Khamisiyah munitions site; 2) subjects from 2 battalions located within a 50-km radius of the Khamisiyah site during early March 1991; 3) subjects from Persian Gulf battalions never located within a 50-km radius of the Khamisiyah site; and 4) subjects from battalions not deployed to the Persian Gulf.

*Aberdeen Proving Ground, Maryland: Follow-Up Investigation of Troops Exposed to Nerve Agents at Aberdeen Proving Ground. DVA/DoD-2VA; DVA/DoD-2DA.*

During 1955-1975, 6,720 U.S. army soldiers participated in an experimental chemical warfare exposure program. To determine the long-term neurological and neuropsychological effects of exposure, a current telephone survey with follow-up clinical examination will be conducted.

*Veterans' Administration Medical Center, Portland, Oregon: G. Kisby, Ph.D. DNA Damage from Chemical Agents and Its Repair. DVA-6D.*

Determine the acute and chronic effects of nitrogen mustard on DNA adducts of human skin tissue and mouse cerebral cortex mixtures.

## **F. Toxicity of Pyridostigmine Bromide.**

*University of North Carolina, Chapel Hill: D.H. Overstreet, Ph.D. Effects of Pyridostigmine in Flinders line Rats Differing in Cholinergic Sensitivity. DoD-33. (Also cited in section B.)*

Examine physiologic and biochemical responses to pyridostigmine in a genetic line of rats with putative supersensitivity to organophosphate nerve agents. Examine if repeated exposure to pyridostigmine protects against short-term body temperature decreases induced by organophosphate cholinergic agents (diisopropylphosphate, chlorpyrifos).

*Purdue Research Foundation: G.E. Isom, Ph.D. Pyridostigmine-induced Neurodegeneration in Rats: Role of Neuronal Apoptosis. DoD-59.*

Description of dose-response relationships for apoptotic cell death in brain regions of rats exposed orally to pyridostigmine. Examination of biochemical and molecular variables in apoptotic cultured cerebellar granule cells exposed to pyridostigmine. Examination of potential linkage between apoptosis and pyridostigmine-induced generation of intracellular reactive oxygen species.

*Midwest Research Institute: M.R. Cook, Ph.D. Individual Differences in Neurobehavioral Effects of Pyridostigmine. DoD- 64.*

Examination of physiological (including blood cholinesterase activities), sensorimotor, and cognitive variables in groups of male and female healthy human volunteers during 2 days immediately after exposure to 13 oral doses of pyridostigmine (either 30 or 60 mg/dose, administered at 8-hour intervals) or placebo. A second study will be conducted under conditions of high ambient temperatures.

*Veterans' Administration Medical Center, East Orange, New Jersey: J. Ottenweller, Ph.D. Effects of Genetics and Stress on Neurobehavioral Responses to Pyridostigmine in Rats. DVA-5D. (Also cited in section F.)*

Examination of neurobehavioral variables (e.g., startle response and behavioral rhythms) in two strains of rats at varying times after exposure to pyridostigmine bromide for 7 days and a 3-day chronic stress regime.

*Veterans' Administration Medical Center, Portland, Oregon: R. Drake-Baumann, Ph.D. Neurotoxicology of Environmental Pollutants and Warfare Agents. DVA-6C.*

Examination of the effects of acute and chronic exposure of pyridostigmine bromide on cholinergic function of spinal cord-dorsal root ganglia-muscle cultures of fetal mice. Examination of the neurological activity of cerebellar explant cultures of newborn mice after two week exposure to sodium bromide.

*Veterans' Administration Medical Center, East Orange, New Jersey: R.J. Servatius, Ph.D. Sensitivity to Pyridostigmine Bromide: Persistent Neural Dysfunction. DVA-49. (Also cited in section B.)*

Determination of pharmacokinetics of pyridostigmine bromide in two genetic strains of rats that differ in inherent levels of butyrylcholinesterase. Comparison of the effects of pyridostigmine bromide and the cholinesterase inhibitors edrophonium and neostigmine on BuChE activity and startle response. Examine the effects of physically-induced stress and pyridostigmine pretreatment on brain acetylcholinesterase activities.

## **G. Assessment/Definition of Gulf War Illnesses**

*Walter Reed Army Institute of Research: Meyerhoff. Combat Stress Diagnosis, PTSD Prevention. DoD-6B.*

Develop methods for early diagnosis of soldiers at risk for combat stress reaction and post-traumatic stress disorder. Measure effect of stress on levels of several hormones (e.g., cortisol, testosterone) in plasma and saliva, and on voice frequency modulation.. Conduct a prospective study of changes in acoustic startle responses and saliva levels of hormones in soldiers subjected to stressful deployments.

*Air Force Institute of Pathology, Washington, DC: LTC D. Dunn. Effects of Gulf War Service on Military Working Dogs. DoD-13.*

Comparison of clinical and pathological assessments of 112 Gulf War-deployed military working dogs and 472 non-deployed military working dogs matched for age, sex, and breed. After military service is completed, dogs will receive complete physical examinations, a neurological examination, a behavioral assessment, a necropsy, and histopathological examinations of samples from leg muscles, nervous tissues, liver, kidney, lung, brain, and fat.

*Walter Reed Army Institute of Research: MAJ J. Stuart. Acute and Long-term Impact of Deployment to Southwest Asia on the Physical and Mental Health of Soldiers and their Families. DoD-23.*

Assess psychological well-being of Army Reserve and National Guard units and their families.

*Klemm Analyses Group: R.J. Klemm, Ph.D. Epidemiological Studies Persian Gulf Illnesses, Persian Gulf Women's Health Linkage Study. DoD-30.*  
Survey of health symptoms in sample of Gulf-deployed and non-deployed female veterans.

*Georgetown University and VA Medical Center, Washington, DC: D. Clauw, M.D. DoD-31. (Also cited in section A.)*

Measure and compare physiologic and biochemical variables in Gulf War veterans with unexplained chronic symptoms, in civilian patients with chronic fatigue syndrome or fibromyalgia, and in healthy controls.

*Veterans' Administration Medical Center, Boston, Massachusetts. R. White, Ph.D. Neuropsychological Functioning in Persian Gulf Era Veterans. DoD-32. (Also cited in section A.)*

Compare results from in-depth neuropsychological evaluations in treatment-seeking Gulf War veterans, non-deployed veterans of Gulf War era, and healthy (non-treatment seeking) veterans. Development and administration of a questionnaire to identify multiple chemical sensitivity.

*University of Texas, SW: R.G. Haller, M.D. Fatigue in Persian Gulf Syndrome-Physiologic Mechanisms. DoD-36.*

Compare physiologic and biochemical variables of muscle function (e.g. oxygen transport and utilization, and enzyme levels) in symptomatic Gulf War veterans with chronic fatigue and asymptomatic "controls".

*VA Medical Center, West Haven CT: S. Southwick, M.D. Psychological and Neurobiological Consequences of the Gulf War Experience. DoD-40.*

Compare memory function over time and magnetic resonance brain images in 20 Gulf War-deployed veterans with PTSD, 20 Gulf War-deployed veterans without PTSD, and 20 non-deployed veterans of the Gulf War era without PTSD.

*University of Pennsylvania: K. Vandenborne, Ph.D. Evaluation of Muscle Function in Persian Gulf Veterans. DoD-41.*

Various measures of skeletal muscle function will be evaluated in Gulf War veterans with unexplained illnesses compared with a control group.

*VA Medical Center, Birmingham, AL: W. Blackburn, Jr., M.D. An Analysis of Risk Factors with an Immunologic and Neuropsychiatric Assessment. DoD-42.*

Case-control evaluation of immunologic and neuropsychological variables and self-reported risk factors in Gulf War veterans with chronic unexplained illness compared with asymptomatic Gulf War veterans.

*University of Cincinnati Medical Science Center: J. Bernstein, M.D. Investigation of Seminal Plasma Hypersensitivity Reactions. DoD-44.*

Examination of blood, semen, and immunological variables in Gulf War veterans and their sexual partners who are experiencing a burning sensation after contact with semen.

*Naval Post-Graduate School, Monterey, CA: H. Bhargava. Exploratory Data Analysis with the CCEP Database. DoD-46.*

Develop a generic computer program to statistically analyze the DoD CCEP database.

*Veterans' Administration Medical Center, Boston, Massachusetts: J. Wolfe. Female Gender and Other Potential Predictors of Functional Health Status Among Persian Gulf War Veterans. DoD-52. (Also cited in section A.)*

Identification and description of self-reported Gulf War environmental and psycho-social combat-theater exposures, functional health status, and health perceptions in a cohort of male and female Gulf War veterans. Development of a survey to identify subjects with multiple chemical sensitivity (MCS)-like symptoms and examination of potential correlations between specific risk factors and MCS-like symptoms.

*Georgetown University and VA Medical Center, Washington, DC: D. Clauw, M.D. Physiologic Effects of Stress in Gulf War Veterans. DoD-57.*

Clinically examine, psychologically evaluate and measure several physiological variables in symptomatic and asymptomatic Gulf War-deployed veterans; evaluate performance in dolorimeter tests and tilt table tests.

*University of Iowa: B. Doebbeling, M.D. Illness Among Persian Gulf War Veterans: Case Validation Studies. DoD-58.*

Administer personal interviews, physical examinations, risk factor assessment, and assessment of neuropsychological, neurophysiological, and psychiatric variables in deployed and non-deployed Gulf War-era veterans. Conduct nested case-control studies of risk factors for various illness classifications.

*University of Texas Southwestern Medical Center, Dallas, Texas: R.W. Haley, M.D. Multi-disciplinary Pathophysiologic Studies of Neurotoxic Gulf War-Related Syndromes. DoD-65. (Also cited in section H.)*

Ask survey questions regarding personality assessments, health symptoms, and wartime exposures to members of a naval battalion that served in the Gulf War. Use two-step factor analysis to identify possible syndromes. Develop a battery of clinical and laboratory tests to assess neurotoxicity (brain or nerve damage) and compare aggregate performance in groups of symptomatic and asymptomatic subjects. Analyze self-reported wartime exposure data and symptom data for statistically significant associations. Develop a plan for conducting a similar survey and clinical examination of a sample of subjects that is based on the entire population of Gulf War veterans.

*Walter Reed Army Institute of Research and Medical Center: C. Engel, Jr., M.D. Replicability of Three Tests for Mycoplasmal Infection of Blood Cells from Symptomatic Gulf War Veterans. DoD-66.*

Compare results from three procedures to detect mycoplasmal infection of blood cells drawn from 60 symptomatic Gulf War veterans: polymerase chain reaction procedure; optimized chelex chain reaction procedure; and nucleoprotein gene tracking procedure.

*Center for Disease Control and States of Pennsylvania and Florida: W.C. Reeves, M.D. Disease Cluster in a Pennsylvania Air National Guard Unit. DHHS-2.*

Determination of a cluster of illnesses among members of the unit. Determination if the cluster was unique to the unit, related to residence in Pennsylvania, or related to Gulf War service. Analysis of survey-collected data on wartime exposures to stressors and multisymptom illnesses to ascertain possible associations. Collection of serum specimens to investigate the presence of possibly unique infectious agents and effects on immune system variables and cholinesterases.

*Boston University School of Public Health: D. Ozonoff, M.D. M.P.H. Cognitive Function and Symptom Patterns in Gulf War Veterans. Cooperative Research Agreement with CDC. DHHS-5.*

Brain activation patterns (from magnetic resonance images) will be analyzed in 40 symptomatic Gulf-deployed veterans, 40 non-symptomatic Gulf-deployed veterans, 40 Germany-deployed veterans of Gulf War era, and 30 treatment-seeking non-deployed veterans. Evaluation of relationships between MRI patterns and levels of cognitive functioning (finger tapping tasks & tests of visual working memory). Mathematical analysis of previously collected symptom data from Gulf War and Germany-deployed veterans to discern if a set of complaints exists that will be useful for determining cause or developing a case definition. Comparison of neuropsychological test performance and symptom prevalence measures in Gulf War-deployed and non-deployed Danish veterans.

*University of Medicine and Dentistry of New Jersey - Robert Wood Johnson Medical School: H. Kipen, M.D., M.P.H. Defining Gulf War Illness. Cooperative Research Agreement with CDC. DHHS-6. (Also cited in section A.)*

Evaluate the persistence and stability of self-reported symptoms in two samples of U.S. Gulf War veterans. Compare the appropriateness of standard working definitions for chronic fatigue syndrome, fibromyalgia, multiple chemical sensitivity with factor-analysis-derived case definitions to describe unexplained illnesses in Gulf War veterans.

*Veterans' Administration Medical Center, Boston, Massachusetts: J. Wolfe, Ph.D.; L. Pepper, M.D. Evaluation of Cognitive, Neurological and Respiratory Functioning of Persian Gulf Veterans. DVA-4A,4B,4D.*

Administration of a health survey questionnaire, an interview about wartime experiences and exposures, a psychological interview, neuropsychological tests examining memory, attention, and learning abilities in a group of 220 Gulf War veterans from Massachusetts, 73 Gulf War veterans from New Orleans, and 50 U.S. veterans deployed to Germany during the Gulf War. Patterns in functional magnetic resonance images of neural tissue will be correlated with performance in tests of motor function and attention in a subgroup of subjects. Possible exposure information for each subject to be evaluated for respiratory function (physical examinations and pulmonary function testing) will be collected from the Army geographical information system and from surveys of occupational history; analysis of the exposure and respiratory function data will search for significant associations.

*Veterans Administration Medical Center, East Orange, NJ: B. Natelson, M.D. Physiological and Psychological Assessments of Persian Gulf Veterans. DVA-5B. (Also cited in section A.)*

Compare physiological, immunological, and neuropsychological variables in healthy veterans, veterans with chronic fatigue syndrome and/or chemical sensitivities, and civilians with chronic fatigue syndrome or chemical sensitivities.

*Veterans' Administration Medical Center, East Orange, New Jersey: N. Fiedler, Ph.D. Effects of Exertion and Chemical Stress on Persian Gulf Veterans. DVA-5C. (Also cited in section A.)*

Examination of effects of acute exhaustive exercise or acute exposure to 5 ppm diesel fumes on psychophysiological variables (e.g., heart rate, blood pressure, respiration rate) and performance in a vigilance task in groups of healthy Gulf War veterans and groups of Gulf War veterans previously diagnosed with fatiguing illness (chronic fatigue syndrome and/or chemical sensitivities).

*Veterans' Administration Medical Center, Portland, Oregon: K. Anger, Ph.D. Psychosocial, Neuropsychological, and Neurobehavioral Assessment of Gulf War Veterans with Unexplained Illnesses. DVA-6A.*

Comparison of performance in a battery of psychosocial, neuropsychological, and neurobehavioral tests by groups of self-reported healthy and ill (with unexplained symptoms) Gulf War veterans.

*Veterans' Administration Medical Center, Portland, Oregon: R. Bennett, M.D. Clinical and Neuroendocrine Aspects of Fibromyalgia. DVA-6B. (Also cited in section H.)*

Evaluate by questionnaire and physical examination the presence of Gulf War veterans with fibromyalgia; using a case-control design, examine relationships between self-reported exposures or risk factors and fibromyalgia; examine neuroendocrine variables in cases and controls.

*Veterans' Administration Medical Center, New Orleans, LA: J. Vasterling, Ph.D. Memory and Attention in PTSD. DVA-10.*

Neuropsychological functions were evaluated in a group of veterans with PTSD, a group of veterans with diagnosed depression, and a group of veterans free of psychopathology. Cognitive functions are to be assessed longitudinally.

*Veterans' Administration Medical Center, Long Beach, California: P.E. Prete, M.D., FACP. Musculoskeletal Symptoms in Gulf War Syndrome. DVA-40.*

Survey with or without physician interview to determine differences in musculoskeletal complaints of peace-time versus Gulf War-deployed veterans.

*Veterans' Administration Medical Center, Tucson, Arizona: I.R. Bell, M.D., Ph.D. Cross-Sensitization as a CNS Model for Gulf War Chemical Intolerance. DVA-48. (Also cited in section A.)*

Comparison of blood pressure, heart rate, and neurobehavioral responses to repeated laboratory exposures to placebo, jet fuel, or perfume in three groups of Gulf War veterans: 1) ill with increased chemical intolerance attributed to military service; 2) ill without increased chemical intolerance; and 3) healthy without chemical

intolerance; and a group of healthy Gulf War-era non-deployed veterans. Measure and compare characteristics associated with enhanced vulnerability to sensitization among these groups.

*Veterans' Administration Medical Center, Cincinnati, Ohio: D. Baker, M.D. Psychobiological Assessment of Desert Storm Veterans. DVA-51.*

Comparison of a series of questionnaires given to 188 treatment and non-treatment seeking Gulf War veterans. Veterans with post-traumatic stress disorder reported greater combat exposure and a higher incidence of physical symptoms.

*Royal Defence Medical College, London: Lt.Col. I.P. Palmer. War Syndromes from 1900 to the Present: Symptom Patterns and Long-term Health Outcomes. DoD-70.*

Examine primary source data from hospital and pension records to compare health symptoms characterized as "War Syndromes" in U.K. and U.S. military units from 1900 to present and determine if a common syndrome can be established using blinded statistical (factor) analysis. Associations between such a common syndrome and risk factors, morbidity, and mortality will be sought using: a case-control analysis using a control group of soldiers receiving a pension for loss of a single limb; an historical narrative analysis of morbidity; and a retrospective cohort analysis of mortality data.

*Social Sectors Development Strategies, Inc., Natick, Massachusetts: Nicole Bell, Sc.D., M.P.H. Post-Deployment Morbid Stress, Behavior and Health; Developing a Model for Predicting Morbidity, Mortality, and Other Adverse Outcomes. DoD-73.*

Using information from the Defense Manpower Data Center Total Army Injury and Health Outcomes Database including Health Risk Appraisals: morbidity of several health outcomes (e.g., hospitalizations for "Gulf War syndrome", CCEP registration, injuries) and mortality will be described for U.S. Army Gulf War veterans. An analysis will be conducted to identify associations between health outcomes and key demographic, behavioral, and stress-related factors. A model will be developed to attempt to predict health outcomes considering predeployment stress variables, predeployment health behaviors, deployment stress variables, and post-deployment variables.

## **H. Disease Prevalence and Associations Between Chemical Exposure and Illnesses in Gulf War Veterans**

*Naval Health Research Center Epidemiology Studies: CDR G. Gray, MC, USN. Epidemiologic Studies of Morbidity Among Gulf War Veterans: A Search for Etiologic Agents and Risk Factors. DoD 1D-1H.*

Comparison of reproductive outcomes (e.g., infertility and miscarriages from questionnaire survey) in randomly selected national samples of Gulf War-deployed and non-deployed U.S. veterans (1D). Historical prospective health survey study of symptoms and illnesses in Gulf-deployed and non-deployed Seabees active between August 1990 & June 1991(1E). Comparison of federal and nonfederal hospitalization rates among veterans who have separated from active service (1F). Comparison of prevalence of congenital anomalies among infants born to Gulf War-deployed veterans, non-deployed veterans, and the non-military population (1G). Establish a DoD birth defects health registry (1H).

*U.S. Army Center for Health Promotion and Preventive Medicine, Aberdeen MD: M.J. Kirkpatrick and J.M. Heller. Development of a Troop Exposure Assessment Model (TEAM)/Health Tracking System. DoD-18; DoD-19.*

Establishment of a geographical information system to establish the geographical location for each Gulf War unit during the time period between January 15, 1991 and date of departure. Expected to be used in assessing site-specific exposure and potential health risks associated with oil fires and other potential chemical exposures.

*March of Dimes, Sacramento, CA.: J.A. Harris, M.D. Feasibility of Investigating Whether There is a Relationship Between Birth Defects and Service in the Gulf War. DoD-35.*

Compare accuracy of DOD hospital records and California Birth Defects Monitoring Program, and determine availability of data for Gulf War-deployed military reserve personnel in the California Birth Defects Monitoring Program.



*King's College, U.K.: S. Wessely, M.D. A Controlled Epidemiological and Clinical Study into the Effect of Gulf War Service on Servicemen and Women of the United Kingdom Armed Forces. DoD-39.*

Assess prevalence of symptoms and unexplained illnesses in Gulf War-deployed U.K. veterans, in non-deployed U.K. veterans of Gulf War era, and in Bosnia-deployed veterans. Administer neuropsychological evaluations to randomly-selected cases with unexplained illness and healthy controls.

*University of Michigan, Ann Arbor: P.F. Pierce, Ph.D., R.N. Physical and Emotional Health of Gulf War Veterans Women. DoD-45.*

Compare the prevalence of general and gender-specific health symptoms in 900 U.S. Air Force Gulf-deployed women and 900 non-deployed U.S. Air Force women.

*University of Oregon Health Sciences: P. Spencer, Ph.D. Persian Gulf Veterans: Epidemiological and Clinical Evidence for Residual Organophosphate Neurotoxicity. DoD-63. (Also cited in section E.)*

Health survey and clinical examination of neuropsychological and neurophysiological variables in a sample of the 20,000 U.S. troops who were located within a 50-km radius of Khamisiyah during the first two weeks of March 1991. Comparison groups will include subjects from other Desert Storm troops, subjects from other Desert Shield troops, subjects from other U.S. military groups that served during, but not in, the Persian Gulf, and civilians with a documented history of exposure to organophosphate insecticides that produced non-convulsive health symptoms.

*University of Texas Southwestern Medical Center, Dallas, Texas: R.W. Haley, M.D. Multi-disciplinary Pathophysiologic Studies of Neurotoxic Gulf War-Related Syndromes. DoD-65. (Also cited in section G.)*

Ask survey questions regarding personality assessments, health symptoms, and wartime exposures to members of a naval battalion that served in the Gulf War. Use two-factor analysis to identify possible syndromes. Develop a battery of clinical and laboratory tests to assess neurotoxicity (brain or nerve damage) and compare aggregate performance in groups of symptomatic and asymptomatic subjects. Analyze self-reported wartime exposure data and symptom data for statistically significant associations. Develop a plan for a similar survey and clinical examination of a sample of subjects that is based on the entire population of Gulf War veterans.

*Institute of Medicine/ Medical Follow-up Agency: P. Renzullo. Five-year Follow-up of Army Personnel Exposed to Chemical Warfare Agents. DoD-69. (Also cited in section E.)*

Compare hospitalization rates and mortality rates during a 5-year, post-Gulf War period among the following groups: 1) subjects from 2 U.S. Army engineer battalions involved with the March 1991 destruction of the Khamisiyah munitions site; 2) subjects from 2 battalions located within a 50-km radius of the Khamisiyah site during early March 1991; 3) subjects from Persian Gulf battalions never located within a 50-km radius of the Khamisiyah site; and 4) subjects from battalions not deployed to the Persian Gulf.

*Center for Disease Control and State of Iowa: D. Schwartz, M.D., M.P.H. Health Assessment of Gulf War Veterans from Iowa. DHHS-1.*

Telephone-survey assessment of prevalence of self-reported symptoms and illnesses in random samples of Gulf War veterans and non-deployed veterans of the same era who listed Iowa as their home. Initial reports found statistically significant higher prevalence of symptoms of depression, Post-traumatic Stress Syndrome, chronic fatigue, cognitive dysfunction, bronchitis, asthma, fibromyalgia, alcohol abuse, anxiety, sexual discomfort, and health-related quality of life in the deployed group compared with the non-deployed group. To validate self report of asthma, a subset of the telephone-survey subjects will be physically examined.

*Veterans' Administration Medical Center, Washington, DC: H.K. Kang, Dr. P.H. Retrospective Cohort Mortality Study of Persian Gulf Veterans. DVA-1.*

Retrospective follow-up mortality study of 697,000 U.S. Gulf War veterans and a reference group of 803,526 U.S. service members of the same era who were not deployed to the Gulf War theater. Analysis of data up to December 1995 indicated that excess mortality rates in deployed veterans was due to death from external causes (e.g., accident, suicide, homicide). Periodic analysis of updated mortality data will occur.

*Veterans' Administration Medical Center, Washington, DC: H.K. Kang, Dr. P.H. VA National Survey of Persian Gulf Veterans. DVA-2.*

Health survey questionnaire mailed to 15,000 Gulf War and 15,000 non-Gulf War U.S. veterans. Telephone contact and interview of 8,000 randomly selected non-respondents to supplement the postal survey and to assess non-respondent bias. Comprehensive physical examination of 2,000 respondents and family members from each group.

*Veterans' Administration Medical Center, Washington, DC: H.K. Kang, Dr. P.H. Use of Roster of Veterans Who Served in Persian Gulf Area. DVA-3.*

For possible exposure assessment purposes, create a database of troop assignments for all U.S. personnel assigned to the Gulf War and of troop locations and movement during deployment.

*Veterans' Administration Medical Center, East Orange, New Jersey: H. Kipen, M.D., M.P.H. Health and Exposure Survey of Persian Gulf Veterans. DVA-5A.*

Postal survey of 2800 Gulf War veterans for self-reported exposure factors and health symptoms. Analysis of the survey data to develop case definitions and conduct case-control analysis to identify possible associations between exposure factors and symptoms.

*Veterans' Administration Medical Center, Portland, Oregon: R. Bennett, M.D. Clinical and Neuroendocrine Aspects of Fibromyalgia. DVA-6B. (Also cited in section G.)*

Evaluate by questionnaire and physical examination the presence of Gulf War veterans with fibromyalgia; using a case-control design examine relationships between self-reported exposures or risk factors and fibromyalgia; examine neuroendocrine variables in cases and controls.

*Veterans' Administration Medical Center, Portland, Oregon: M. Riscoe, Ph.D. Clinical and Epidemiological Leishmania Research. DVA-6E.*

Serological testing for the prevalence of leishmania in a random sample Gulf War veterans and controls.

*Naval Health Research Center, San Diego, California: C.G. Blood. A Comparison of Post Deployment Hospitalization Incidence Between Vietnam and Gulf War Veterans. DoD-71.*

Comparison of post-deployment hospitalization rates in Gulf War veterans and Vietnam veterans. Data will be gathered from medical history and physical examination board databases of the Defense Manpower Data Center.

*Duke University Medical Center: J.A. Fairbank. Relationships of Stress Exposures to Health in Gulf War Veterans. DoD-74.*

National samples of Gulf-deployed and non-deployed U.S. veterans will be surveyed for information on demographics, health conditions, psychological functioning, and illnesses. Subjects will be classified as cases with multiple symptoms or non-cases, and a subsample of Gulf-deployed and non-deployed cases and non-cases will be interviewed to obtain information about military experiences, pre-military and pre-deployment activities, risk factors, and protective factors. Statistical analysis will look for associations between Gulf War illnesses and various potential health risk factors related to stress.

## **I. Toxicology of Depleted Uranium**

*Inhalation Toxicology Laboratory, Albuquerque New Mexico: F. Hahn, Ph.D. Carcinogenicity of Implanted Depleted Uranium Fragments in Rats. DoD-7B.*

Evaluation of the presence of tumors in muscles of rats with 2-year exposure to muscle-implanted depleted uranium fragments.