GULF WAR EXPOSURES AND UNEXPLAINED ILLNESS:

A COMPARISON OF

ENLISTED AND OFFICER EXPERIENCES

By

Kathryn Kay Ellis

A Thesis

Presented to the Department of Public Health and Preventive Medicine

and the Oregon Health Sciences University

School of Medicine

in partial fulfillment of

the requirements for the degree of

Master of Public Health

April 2004

Department of Public Health and Preventive Medicine
School of Medicine
Oregon Health and Science University

CERTIFICATE OF APPROVAL

This is to certify that the MPH Thesis of

Kathryn Kay Ellis, MD

has been approved.

[redacted]

Jodi Lapidus, PhD
Professor in charge of thesis

[redacted]

William Morton, MD, DrPH.
Member

[redacted]

Linda McCauley, PhD, RN, FAAN
Member

TABLE OF CONTENTS

LIST OF TABLES

ACKNOWLEDGEMENTS

I would like to thank my thesis advisor, Jodi Lapidus, PhD, and my committee members, William Morton, MD, DrPH, and Linda McCauley, PhD, RN, FAAN, for their expertise and guidance. Michael Lazarus, MS deserves gratitude for providing me with the data sets used for this project. I would also like to thank the staff of the Department of Public Health and Preventive Medicine who enabled me to complete this study from long distance.

Lastly, I would like to acknowledge those units with which I served in the second Persian Gulf War while writing this thesis, the 109th Area Support Medical Battalion, the 21st Combat Support Hospital, and the 101st Air Assault Division, whose example of endurance and self-sacrifice provide me with the motivation to promote veterans' health.

ABSTRACT

Symptoms of unexplained illness have been reported by approximately 15,000 Gulf War (GW) veterans to either the Veterans' Affairs (VA) or Department of Defense (DoD). Enlisted personnel are disproportionately affected. Numerous toxins as well as physiologic and psychological stressors have been considered as possible etiologic factors.

The object of this experiment was to quantify the contribution of chemical and a physiologic stress (heat) toward the increased risk of unexplained symptoms in enlisted GW veterans. Two data sets used in prior GW studies were merged for this study. Subjects included 1959 enlisted and 263 officers. Chi-square tests of homogeneity were used to determine the association between rank and potentially toxic exposures, and between unexplained symptoms and these exposures, stratified by enlisted or officer status. The mean number of exposures was examined using ANOVA. Finally, a series of logistic regression models was used to determine if the odds ratio (OR) of unexplained symptoms among enlisted relative to officers would be reduced by the addition of chemical exposures, and the further addition of heat stress, to the model.

The chi-square analyses showed that enlisted personnel were more likely to have reported handling petrochemical fuel (OR 3.07, 95% CI 2.36-4.00), using DEET insecticide cream (1.35, 1.04-1.76), spending at least 12 hours outside per day (1.32, 1.01-1.71), and experiencing physical reactions to sun exposure (2.78, 2.10-3.68). Enlisted personnel were less likely to have reported petroleum sprayed in their compound (0.63, 0.49-0.84). There was no difference between officers and enlisted in the number of persons who reported exposure to oil well fires, lindane, permethrin, flea collars, or

pyridostigmine bromide (PB). Every exposure variable was significantly related to unexplained symptoms among enlisted subjects. Only handling petrochemical fuel and experiencing a heat stress symptom were significant among officers.

The mean number of chemical exposures was observed to be similar for both officer and enlisted control groups at 2.52 (2.25-2.79) and 2.49 (2.36-2.63) respectively. The analogous values for officer and enlisted case groups were 3.15 (2.66-3.63) and 3.43 (2.70-3.62). Tukey HSD demonstrated that the mean difference between the groups was significant for case/control status, but not enlisted/officer status. The OR of enlisted relative to officers reporting unexplained symptoms was 2.69 (1.74-4.16), and remained virtually unchanged when chemical exposures were added to the logistic regression model. When the heat stress variable was added to the model, the OR decreased to 2.10 (1.27-3.24).

These results suggest that sun/heat exposure may be partially responsible for the higher prevalence of unexplained symptoms among enlisted GW veterans. The associations between exposures and unexplained symptoms were stronger for enlisted personnel than for officers, and the total number of chemical exposures may be associated with unexplained illness among both enlisted and officers. However, there was no evidence that chemical exposures contribute to the increased risk of unexplained illness among enlisted GW veterans.

INTRODUCTION

Approximately 697,000 men and women served in Operation Desert Shield/Desert Storm between August 1990 and June 1991 (IOM, 1996; PAC, 1996). Air attacks against the Iraqis began on January 16, 1991. The ground war lasted only 5 days from February 24 until February 28, at which time the Iraqis were defeated and peace was restored. Two hundred ninety-five deaths occurred among United States (US) troops, 148 due to combat and 145 from accidents or disease. A total of 467 US soldiers were wounded.

In 1992, several members of an Indiana Army National Guard unit who had returned from the Gulf War (GW) reported a variety of subjective complaints including fatigue, trouble concentrating, muscle and joint pains, and headache (PAC, 1996). The Department of Defense (DoD) sent in an epidemiologic research team, but no evidence of an outbreak was found. However, the issue received significant media coverage, abroad as well as in the US, and many more US and United Kingdom (UK) veterans of the PGW complained of chronic vague symptoms.

A health registry for GW veterans returned to civilian life was established by the Department of Veterans Affairs (VA) in August 1992. In June 1994, the DoD established the Comprehensive Clinical Evaluation Program (CCEP). More than 100,000 GW veterans with health concerns have registered with either the VA or the DoD by calling a toll-free number (VA website, 2003). The reporting veteran received a comprehensive clinical evaluation performed by multiple specialists. Most have been given concrete diagnoses such as sprained ankle, but greater than 15,000 (approximately 20%) complained of symptoms for which no medical explanation has been found.

In 1994, the US Secretary of Defense, the Secretary of Veterans Affairs, and the Commonwealth of Pennsylvania asked the Centers for Disease Control and Prevention (CDC) to investigate a "mysterious illness" affecting GW veterans from a Pennsylvania Air National Guard unit (Fukuda et al, 1998). The CDC researchers surveyed and examined the index unit, and compared them with survey data obtained from 3 other study groups: 1.) Another Air National Guard unit from Pennsylvania, 2.) Air Force Reserve personnel, and 3.) Active Air Force personnel. Using factor analysis of the data collected from the 3255 total participants, the researchers developed a case definition for a chronic multisymptom illness of GW veterans. A case must have had 1 or more symptom from at least 2 of 3 categories (fatigue, mood-cognition, and musculoskeletal), present for at least 6 months. The CDC did not find any association with specific GW exposures, and the illness was also present among nondeployed personnel, though in lower prevalence (45% among deployed personnel vs. 15% among nondeployed).

The VA has been providing compensation payments to chronically disabled GW veterans with undiagnosed illness since 1995 (VA website, 2003). However, a soldier is expected to be more concerned with the welfare of the group than with his own (Waitzkin & Waterman, 1974). Therefore, social pressure may prevent some ill troops from seeking medical attention.

In 1996, the results of 2 research committees were published, the Presidential Advisory Committee (PAC) on Gulf War Veterans' Illness and the Institute of Medicine (IOM) Committee to Review the Health Consequences of Service during the Persian Gulf War. The PAC reported receiving public comment that GW veterans seeking care for their symptoms at DoD and VA facilities were given the message that their problems were all in their heads. Some staff at medical facilities interviewed by the PAC expressed concern that the structured evaluations of the registry may reinforce the sick role.

The IOM cited poor military record-keeping as an obstacle to the investigation of GW veterans' health concerns. No records were kept of environmental exposures, and soldiers' personal medical records were often incomplete. Even vaccine records were sometimes inaccurate.

The Post-Deployment Health Evaluation and Management Clinical Practice Guideline (PDH CPG) was developed to improve surveillance as well as care of the individual soldier (DHCC website, 2003). It provides a systematic basis for the evaluation and treatment of soldiers with health concerns related to deployment. Voluntary registration with the CCEP is no longer necessary because deployment-related diagnoses are now entered and monitored electronically. Instead of the multi-specialist clinical exam, soldiers with deployment-related concerns are encouraged to first visit their military primary care provider to prevent fragmentation of care and receive better follow-up.

Comparison with Other Wars

A post-combat syndrome characterized by unexplained medical symptoms is not unique to the PGW, but rather has been identified after all modern wars (Hyams et al, 1996; Jones et al, 2002). Following wars of the 19th and early 20th century, US soldiers reported a wide variety of somatic symptoms, but cardiac complaints were predominant. A researcher named Da Costa described and treated a syndrome during the US Civil War that he called "irritable heart". A similar illness of WWI and WWII was named "effort syndrome" because the cardiac symptoms appeared to worsen with strenuous activity. It was observed that soldiers with effort syndrome improved with a graduated exercise program and encouragement from staff, but telling the patient that he had a heart condition hindered recovering. As it became believed during WWII that this combat-related heart disease was psychosomatic, neuropsychiatric symptoms began to replace cardiac complaints. Jones et al (2002) suggest that the form a post-war syndrome takes is influenced by advances in medical science, changes in the nature of warfare, and underlying cultural forces. "Gulf War Syndrome", with its prominent neurologic, cognitive, and psychiatric symptoms, is a likely evolution of the post-combat illness of WWII.

A post-war somatic syndrome has not been identified among Vietnam veterans, perhaps dwarfed by the large prevalence of Post-Traumatic Stress Disorder (PTSD) in this group. When completing survey questionnaires for studies of Agent Orange, Vietnam veterans will often mark neurological symptoms similar to those reported by GW veterans. A post-war syndrome has also not been observed among veterans of the Bosnian conflict (Unwin et al, 1999). However, perceived danger and other stresses for US soldiers in Bosnia were probably significantly less than for soldiers in SW Asia. A study by Rand's National Defense Research Institute found that re-enlistment rates actually increase following 3 month overseas deployments involving some danger, such as in Bosnia (Corpus Christi Caller Times website, 2004). Morale and re-enlistment rates begin to decline as the deployment lengthens and the danger level rises.

The Influence of Gender on Symptom Reporting

In civilian populations, women are more willing to report health symptoms and use health services than men (Nathanson, 1975, 1980). Research on the association between unexplained illness (UI) of GW veterans and female gender have had mixed results. In a 1992 Indiana study by DeFraites et al, the prevalence of unexplained symptoms among male and female reserve troops was similar (DeFraites et al, 1992). A 1995 study of reservists by Sutker et al found more females than males reported physical or somatic symptoms such as headaches, fatigue, and upset stomach, regardless of deployment status. Spencer et al (2001) found an elevated risk of UI among women.

In one study performed immediately after the subjects returned from the Gulf, females were found to have higher PTSD scores. Wolfe et al (1993) suggests that this may be due to women reporting symptoms more freely than men, prior victimization, and/or sexual harassment or assault during deployment. More physical symptoms are reported by women with PTSD (Wolfe et al, 1995), suggesting that some of the physical symptoms reported by female PGW veterans may be related to PTSD.

Prior abuse, coupled with combat stress may affect men and women differently (IOM, 1996). Female veterans who reported previous abuse were found to have higher PTSD and depression scores in a study by Engel et al (1993), while abused male veterans did not differ from nonabused in PTSD symptoms. Another study found no differences between male and female veterans in PTSD indicators for noncombat reservists, but gender differences were observed in 2 combat units (Perconte et al, 1993). One of these units had experienced fatalities and injuries from a SCUD missile attack and the other had morale problems.

PGW Exposures

The desert environment of the PGW theater included high temperatures, extremes in rain fall, blowing sand, insects, animals, and smoke (IOM, 1996; PAC, 1996). In these harsh conditions, troops performed strenuous physical labor and were vulnerable to illness and injury. In addition, deployed soldiers were exposed to a number of chemicals, including agents meant to protect the troops such as insecticides, vaccines, and nerve agent pretreatment. Psychological stressors included scud attacks, seeing dead or injured persons, leadership or morale problems, and separation from family. The following exposures were examined as risk factors for unexplained illness by the IOM and PAC.

Oil Well Fire Smoke - At the end of the GW, retreating Iraqi soldiers ignited more than 600 Kuwaiti oil wells and several pools of spilled oil. The smoke sometimes remained low to the ground, enveloping US military personnel.

Petroleum Products - Many petroleum-based fuels were used during the gulf war for dust suppression, heaters, portable generators, fueling vehicles, etc. Some individuals in certain jobs were exposed to fuel vapors and combustion products such as sulfur dioxide, nitrogen dioxide, and particulates.

Depleted Uranium (DU) - Naturally occurring uranium is chemically toxic, radioactive, and is composed of three isotopes. DU is the byproduct created by removal of the isotope used in nuclear reactors and weapons. It is twice as dense as lead, and therefore is used for armor, such as that of tanks, and for munitions. DU exposure could result from retained shrapnel secondary to friendly fire, from accidental munitions fires, or from being inside an armored vehicle while it is struck with munitions. The substance has been known to cause kidney toxicity and has a low level of radioactivity.

Pesticides and Insect Repellents – Insecticides such as DEET, permethrin, and organochlorine (lindane) were shipped by the DoD to the Gulf region for use during the war. DEET was issued to troops as a cream to be applied directly to the skin. Permethrin is sprayed only onto equipment and clothing due to potential neurotoxicity. Lindane is used for treatment of scabies and lice. Some soldiers used flea collars on equipment or worn on their body.

Infectious Diseases - Shigellosis, malaria, sandfly fever, and leishmaniasis are endemic in the Gulf region. However, prevention was emphasized and cases of infectious diseases were low during the 1990-91 PGW (Hyams et al, 2001; IOM, 1996; PAC, 1996).

Biological Weapons - It is believed that Iraq possessed, though did not use, anthrax, botulism toxin, and aflavotoxin for use as weapons (IOM, 1996; PAC, 1996). There are no known chronic health effects due to anthrax or botulism infection. Aflavotoxin is a toxic metabolite produced by fungus. Its only known long term health consequence is liver cancer.

Vaccines – Numerous vaccines are indicated for deploying soldiers (Deploymentlink website, 2004). Routine childhood immunizations including measles/mumps/rubella (MMR), polio (OPV or IPV), tetanus/diphtheria (Td), varicella, and hepatitis B are administered unless records indicate that these are up to date. Due to living in close quarters, soldiers are at high risk for influenza and meningitis, so receive flu and meningoccal vaccines. Travel immunizations such as hepatitis A and typhoid (oral or IM) are given, as well as vaccines against biological weapons such as anthrax. Anthrax vaccine was FDA licensed in 1970 for use in those with occupational exposure to animal hides and wool (IOM, 1996; PAC, 1996). Botulism toxoid is no longer routinely administered to troops deploying to the Persian Gulf, but was given to some soldiers during the 1990-91 PGW. The vaccine has been used for 25 years by those with potential exposure through industry or laboratory. It is still in the investigational status. The safety records of anthrax and botulism toxoid vaccines for civilian use have given no cause for concern.

A study of UK servicemen found that, among GW veterans, vaccinations against biological warfare agents and greater than 7 routine vaccinations were associated with the CDC case definition for multisymptom syndrome (Unwin et al, 1999). However, there was no association between vaccines and the CDC multisymptom syndrome among veterans who had deployed to the Bosnia conflict. An interaction effect between stress and multiple vaccinations is plausible since the neuropsychiatric and immune systems are linked through the endocrine system (Rook and Zunla, 1997). It has been postulated that cytokines induced by some vaccines may induce somatic symptoms, especially in individuals under stress.

Chemical Warfare Agents - US forces believed that Iraq possessed both nerve agent and mustard agent during the Gulf War (IOM, 1996; PAC, 1996). Nerve agents are organophosphates, which cause cholinergic over-activity by inhibition of acetylcholinesterase. Death occurs by respiratory arrest secondary to inhibition of the respiratory center of the brain, respiratory muscle paralysis, and excessive mucous secretion. The agents can be in gas, aerosol or liquid form, and are usually inhaled or absorbed through the skin. Atropine and pralidoxime chloride (2PAMC1) are antidotes carried by soldiers in the form of autoinjectors. Pyridostigmine bromide (PB) can be used as a pretreatment and is discussed later.

Mustard agent produces chemical burns (PAC, 1996). The skin, eyes, respiratory, and gastrointestinal tracts can be affected. Iraq used mustard agent against Iran in 1984. Five thousand casualties resulted with first to third degree burns over 20 to 70 percent of the total skin surface. During the GW a presumptive diagnosis of mustard poisoning was made for one US military personnel who developed small chemical burns on his arms while patrolling an Iraqi bunker during the war. No other cases of injury or illness due to chemical warfare exposure were detected by medical surveillance in the Gulf region.

Some organophosphate pesticides no longer sold in the United States have been shown to cause organophosphate-induced delayed neurotoxicity (OPIDN) after low dose exposure (IOM, 1996; PAC, 1996). Symptoms begin with lower extremity weakness and can be progressive. Testing of chemical warfare agents has not found them capable of producing OPIDN. However, severe exposure may result in subtle, long-term, neuropsychological abnormalities such as slightly reduced intellectual functioning and simple motor skill deficits (IOM, 1996).

In March 1991 after the ground war concluded, a large enemy munitions storage depot was destroyed with explosives by US personnel in Khamisiyah, Iraq. The United Nations Special Commission on Iraq (UNSCOM), sent to find and destroy biological and chemical weapons, later learned that sarin had been stored at the Khamisiyah demolition site (Gulflink website, 2004). Atmospheric modeling determined that approximately 102,000 troops were potentially exposed to low levels of the nerve agent. The estimated concentration of sarin was too low to produce symptoms such as OPIDN. However, the possibility of adverse health effects resulting from the combination of sarin with other noxious chemicals or stressors has not been ruled out. In a 2001 study by McCauley et al, soldiers who witnessed detonations at Khamisiyah reported more psychoneurological symptoms than soldiers deployed elsewhere in SW Asia during the combat period. No excess symptoms were observed among soldiers who were within 50 km of the Khamisiyah Ammunition Storage Point but did not witness the detonations.

A survey of 249 naval reservists by Haley et al, 1997 found a cluster of individuals who reported symptoms suggestive of central and peripheral nervous system damage. Neurological testing of 23 cases with the most severe symptoms compared with 10 well GW veterans and 10 nondeployed controls produced findings consistent with delayed neurotoxicity secondary to organophosphate exposure (Haley et al, 1997; Haley and Kurt, 1997). From a subsequent study of the same subjects, Haley et al (1999) reported that GW veterans with neurologic symptoms had low activity levels of type Q paraoxonase/arylesterase (PON-Q), a genetically regulated enzyme which hydrolyzes some organophosphates such as sarin. Twelve subjects with the worst audiovestibular dysfunction received magnetic resonance spectroscopy which reportedly showed reduced functioning neuronal mass in the left basal ganglia, compared to 15 healthy veteran controls (Haley et al, 2000).

Pyridostigmine Bromide (PB) - This medication was used by some units as a pretreatment against nerve agent poisoning (IOM, 1996; PAC, 1996; OPCW website, 1999; USAMRICD website, 1999). PB is effective only against soman, one type of nerve agent. The drug is FDA approved for use in the treatment of myasthenia gravis. One pill binds with and inhibits approximately 25 percent of the acetylcholinesterase in the body and releases the enzyme at a slow steady state. The soman binding site is blocked when PB is bound.

Animal studies have led some researchers to a hypothesis that stress may interact with anticholinesterases such as PB and some insecticides to produce the symptoms reported by GW veterans (Friedman et al, 1996; Kaufer et al, 1998). Friedman et al demonstrated in 1996 that PB crosses the blood-brain barrier only under stressed conditions. A 1998 study by the same investigaters suggests that a feedback mechanism to subdue the response to stress may produce delayed neurologic symptoms. Stress triggers a transient increase in the release of acetylcholine which results in a phase of enhanced neuronal excitability (Imperato et al, 1991). In a compensatory mechanism to quiet the brain after stress, the expression of genes involved in acetylcholine metabolism is promoted (Friedman et al, 1996; Kaufer et al, 1998). Acute stress and pharmacologic blockade of acetylcholinesterase were shown in animals to produce long-lasting changes in the expression of these genes, which could result in long-term decreased levels of available acetylcholine (Kaufer et al, 1998).

PB was issued to GW troops as a blister pack containing 21 pills. Spencer et al, 2001, found that recall was improved when subjects were asked the number of packets of PB completed rather than the number of pills. UI was associated with the number of side effects reported by subjects rather than the severity of side effects, which led the investigators to suspect that the association was due to somatization rather than causation.

Psychological Stress – Combat stress and civilian life stresses aggravated by deployment (marital strife, financial difficulties, etc) are plausible causes of "Gulf War Syndrome". Quantitative measures of combat stress such as the Keane Combat Score have been used in previous studies of unexplained symptoms in GW veterans (Bourdette et al, 2001; Spencer et al, 2001). As stated above, stress may interact with chemical and/or physical stressors to produce somatic symptoms (Friedman et al, 1996; Kaufer et al, 1998; Rook and Zumla, 1997).

Physiologic Stress (Heat, Labor, and Medical Illness or Injury) - Symptoms of health problems while working in the sun such as dizziness, muscle cramps, disorientation, etc. were found to significantly increase the odds ratio (OR) of reporting unexplained symptoms in GW veterans (Spencer et al, 2001). Having sought medical treatment for and illness or injury was also associated with unexplained symptoms.

In general, PGW studies have found that when examined singularly, most of these exposures are associated with unexplained symptoms. However, due to significant correlation between exposures, most do not remain significant when examined in a multiple regression model (Iowa Persian Gulf Study Group, 1997; Spencer et al, 2001; Unwin et al, 1999). As stated previously, research has had to rely on recall by veterans because environment exposures were not well documented during the 1990-91 PGW (IOM, 1996). Exposure information is now collected from the soldier during the Post-Deployment Health Evaluation and stored electronically (DHCC website, 2003).

The Influence of Rank

In the 1998 PGW Survey conducted by the Portland Veterans Affairs Medical Center (VAMC) and the Center for Research on Occupational and Environmental Toxicology (CROET) at Oregon Health and Science University (OHSU), it was noted that 12 percent of responding enlisted soldiers reported unexplained symptoms, compared to only 3 percent of officers (Spencer et al, 2001). The association between enlisted rank and unexplained illness is consistent with previous studies of GW veterans (Fukuda et al, 1998; Nisenbaum et al, 2000). This finding is also consistent with broader observations of the association between health and socioeconomic status (Lantz et al, 1998; Marmot and Wilkinson, 1999). The correlation between increased prevalence of nearly all diseases and low socioeconomic status is thought to result from the interaction of multiple physical and psychosocial factors. The difference between enlisted and officers in the prevalence of unexplained illness in GW veterans will probably never be fully explained due to the complex nature of the relationship between social status and health.

However, it is plausible that enlisted status is correlated with 1 or more chemical and/or physical exposures which may increase of the risk of unexplained symptoms. Enlisted personnel perform more physical labor such as loading and unloading of equipment, setting up tents, digging fox holes, etc. Most of this labor is performed outdoors with exposure to sun, heat, and insects. Enlisted soldiers are also more likely to have occupations that require exposure to petroleum products, such as truck driver or mechanic. Psychological stress may be increased among enlisted personnel due to lack of control. PB and vaccines would not be expected to be associated with enlisted status because administration is determined by geographical area of deployment.

OBJECTIVES

A secondary analysis of 2 Gulf War veterans surveys was conducted by combining responses from the OHSU/CROET Persian Gulf War (PGW) Survey and the OHSU/CROET Khamisiyah Veterans Survey. The objectives of this study were to:

1.) Determine if there is an association between enlisted rank and potentially toxic environmental exposures.

2.) Determine if these exposures are individually associated with unexplained symptoms in a.) enlisted, b.) officers, and c.) all GW veterans, adjusted for rank

3.) Determine if the total number of chemical exposures is associated with unexplained symptoms in GW veterans.

4.) Quantify how much of the increased risk of unexplained symptoms in GW enlisted veterans can be attributed to chemical exposures and a physical exposure (sun/heat stress). The expected outcome was that the OR of enlisted GW veterans to officers with unexplained symptoms would decrease as chemical exposures and heat stress were added to the logistic regression model. However, some residual, unexplained, elevated risk in enlisted GW veterans would likely remain.

MATIERIALS AND METHODS

Study Population

Subjects for both the Khamisiyah and PGW studies were drawn from an Operation Desert Shield/Desert Storm (ODS/S) database provided by Defense Manpower Data Center and maintained by the DoD. The PGW database received for this investigation contained 978 subjects and the Khamisiyah database had 1779 subjects. However, 516 of the Khamisiyah subjects were not deployed and therefore were excluded. From the total 2241 subjects remaining, 19 were excluded from subsequent analyses because *rank* was missing, leaving 2222 subjects. Enlisted personnel accounted for 1959 and 263 were officers.

The population of the PGW study was deployed to SW Asia within the 1-year period after August 1990. They came from all branches of service and listed either Oregon or Washington as their home-state-of-record at the time of deployment. A random sample of male veterans and all eligible female veterans were mailed survey questionnaires. A response rate of 64% for locatable veterans and a 55% total response rate for all mailed surveys were achieved. Responders were more likely than non-responders to be Caucasian, female, to have served in an active reserve unit, and to have served in the army branch. Selection is described in more detail elsewhere (Bourdette, 2001; Spencer et al, 2001).

Subjects retained from the Khamisiyah database for this study were present in the area of Khamisiyah, Iraq in March 1991 at the time of the munitions detonation and potential sarin exposure, and those deployed elsewhere in SW Asia during the 1990-1991 Gulf War. The latter group was used as deployed controls for the original study. All subjects resided in Oregon, Washington, California, North Carolina, or Georgia and served in the US Army or Army National Guard. Eighty-one percent of those contacted agreed to be interviewed by computer-assisted telephone survey. Those agreeing to participate in the interview were more likely to be older, female, and Caucasian than nonparticipants. See McCauley et al, 2001 and McCauley et al, 2002 for further details.

When a 2X2 contingency table of the combined PGW and Khamisiyah study population was created for rank and gender, officers were found more likely to have been female than enlisted ($p<0.001$). Minorities are more likely to be enlisted, and the army is over-represented among both enlisted and officer. Table 1 demonstrates demographic information. Due to missing data, some totals do not add up to 2222.

In both original studies, subjects were given a clinical examination to confirm health symptoms and rule out explainable diagnoses. However, the current study uses only data obtained from the survey questionnaires. Reliability was assessed in the original studies by re-questioning a random sample of Khamisiyah veterans 6 months after completing the initial survey, and a random sample of PGW veterans were re-tested at the time of clinical examination.

The 8 chemical exposure variables used are listed in Table 2. Measures of sun/heat exposure, including symptoms of heat-related illness and hours spent outside per day, are in Table 3. A single variable measuring sun/heat exposure symptoms called *heat stress* was created because the symptom variables are likely to be correlated. The *>12 hours outside* variable was included for validity. Both of these measures of heat exposure have advantages and limitations. *>12 hours outside* may be less subjective than *heat stress* because it has an unequivocal quantitative boundary (12 hours) between affirmative and negative response. However, heat-related illness is also influenced by the degree of strenuous activity and amount of clothing worn. *Heat stress* accounts for these while shift length (*>12 hours outside*) does not.

All responses were converted to binary variables for the analyses. Vaccines and depleted uranium variables were not included in the analyses due to poor reliability (Spencer et al, 2001). Possible responses to the question concerning rank were only 'enlisted' or 'officer'. Warrant officers, a group with hierarchal status between that of enlisted and officers, are becoming less common in the military as they are merged into the officer class. Therefore, warrant officers were counted as officers.

Table 2. Chemical Exposure Variables obtained from OHSU/CROET PGW and Khamisiyah Study Data Sets.

Exposure Variable	Question Asked or Description	Binary Response
Petroleum sprayed	Petroleum solutions sprayed in your compound to keep dust down?	Yes No
Diesel handled	Handled diesel or other petrochemical fuel?	Yes No
Proximity to oil well fire	How close were you to oil well fire?	< 1 mile > 1 mile
PB	# packs of PB completed (21 pills per pack)	>1 pack < 1 pack
Lindane	Used lindane?	Yes No
Insecticide cream	Applied government-issued insecticide cream to skin? (DEET)	Yes No
Insecticide spray	Applied government-issued insecticide spray to clothing? (Permethrin)	Yes No
Flea collar	Wore flea collar on body?	Yes No

Table 3. Sun/Heat - related Variables obtained from OHSU/CROET PGW and Khamisiyah Study Data Sets.

Exposure Variable	Question Asked or Description	Binary Response
Sunburn	While working in the sun, did you experience a sunburn causing blisters?	Yes No
Dizziness	Experience dizziness while working in the sun?	Yes No
Light-headedness	Experience light- headedness while working in the sun?	Yes No
Muscle cramps	Experience muscle cramps while working in the sun?	Yes No
Disorientation	Experience disorientation while working in the sun?	Yes No
Dehydration	Experience severe dehydration while working in the sun?	Yes No
Loss of Consciousness (LOC)	Experience LOC while working in the Sun?	Yes No
Heat Stress	At least 1 of the above heat-related symptoms while working in the sun	Yes No
>12 hours outside	Spend at least 12 hours outside per day	Yes No

Case Definition

A case definition was created from symptoms asked on both the PGW and Khamisiyah surveys. In the original studies, those subjects giving affirmative answers to any of these symptoms received clinical examinations, and a designation of case or control was made based on the results of the examination. Cases in the PGW study were those who met the Portland Environmental Hazards Research Center (PEHRC) definition (Bourdette et al, 2001), which was reporting 1 or more chronic symptoms from at least 1 of the following 3 categories:

Cognitive

Difficulty with speech

*Insomnia

*Changes in memory

*Mood Swings

*Depression

Anxiety

Difficulty learning new things

Musculoskeletal

Back pain

*Persistent muscle aches

Painful joints

Swollen joints

Joint Stiffness

Pain after exertion

Fatigue

*Unexplained fatigue and at least 4 of the following:

Chills/fever

*Headache

*Unrefreshing sleep

*Tender glands

*Changes in memory

*Difficulty concentrating

*Sore throat

*Painful joints

*Unexplained weakness

*Fatigue after exercise

*Persistent muscle aches

The CDC case definition for chronic multisymptom illness requires 1 or more symptom from at least 2 of the preceding three categories, present for at least 6 months (Fukuda, 1998).

Case/control assignment in the current study is based on the CDC definition. Some symptom information was obtained during the clinical exam phase of the original Khamisiyah and PGW studies, so was not present on the databases used by this investigator. A symptom was not used if it was available from only 1 of the 2 data sets. The Khamisiyah data was the more limiting of the 2. Asterisk (*) denotes those symptoms which were available on both databases and therefore used in the current study. Also, the questionnaires asked subjects to report symptoms present for at least 1 month rather than the 6 months chosen by the CDC to define chronic. Regardless, subjects in this study have unexplained prolonged somatic symptoms that began during or after deployment to the Persian Gulf. The CDC definition should not be considered a gold standard since the exact nature and presentation of multisymptom illness in GW veterans is still under study.

Statistical Analyses

SPSS statistical software was used for all statistical analyses except power and sample size calculation, for which PASS was used. Chi-square tests of homogeneity were performed with officer versus enlisted status against the variables: *petroleum sprayed, diesel handled, proximity to oil well fire, PB, flea collar, insecticide spray, insecticide cream, lindane, dehydration, loss of consciousness (LOC), disorientation, muscle cramps, light-headedness, dizziness, sunburn, heat stress, and >12 hours outside.* See Tables 3 and 4 for description of exposure variables. A crude OR was calculated for each exposure. Gender was compared to officer versus enlisted status for preliminary examination of the potential of gender as a confounder. Contingency tables were also made of each exposure variable versus case/control status, stratified by rank, to evaluate the individual association between the exposure and unexplained symptoms separately for enlisted personnel and officers. The pooled OR was calculated using the Mantel-Haenszel method. Power calculation was performed to assess the adequacy of officer sample size for stratified chi-square analyses.

One-way ANOVA was used to determine if the total number of exposures is associated with unexplained symptoms or rank. Four study groups were made: 1.) Officer cases, 2.) Officer controls, 3.) Enlisted cases, and 4.) Enlisted controls. The total number of chemical exposures was calculated for each subject, and used as the dependent variable. The hypothesis was that the mean number of exposures of the 2 case groups would be significantly higher than the 2 control groups.

A series of logistic regression analyses was used to determine how much of the increased risk of unexplained symptoms in enlisted can be attributed to chemical exposures and sun/heat exposure. First, the crude OR was determined for the variable *rank* (enlisted/officers) using simple logistic regression. The chemical exposure variables were then added to the model, and the *rank* OR compared to that of the simple model. A change in the OR would indicate that the added variables are confounders that contribute to the difference in risk between enlisted and officers. Finally, *heat stress* was added and the *rank* OR re-examined. *Heat stress* was chosen to represent sun/heat exposure in the regression analyses instead of the *>12 hours outside* variable because the latter does not account for risk factors of heat-related illness other than shift length outdoors.

Treatment of Missing Data

Many of the subjects had missing exposure or symptom data. If the missing data was not used in the statistical analysis being performed, the subject was retained for that analysis. Therefore, few subjects were eliminated for missing data in the preliminary chi-square analyses when exposure variables were examined singularly. However, the *n* decreases from the total of 2222 in subsequent statistical analyses because multiple exposure and symptom data were required. ANOVA and logistic regression used every exposure and every symptom, and consequentially *n* decreased to 1033 with 876 enlisted and 157 officers. Table 4 displays the demographic characteristics of the study population after the exclusion of all subjects with missing data.

Table 4. Demographic Characteristics of Subjects after Exclusion of Missing Data.

	Enlisted	**Officers**	**Total**
Gender			
Male	832 (95.0%)	141 (89.8%)	973 (94.2%)
Female	44 (5.0%)	16 (10.2%)	60 (5.8%)
Race			
Caucasian	645 (73.6%)	131 (83.4%)	776 (75.1%)
African-American	138 (15.8%)	12 (7.6%)	150 (14.5%)
Hispanic	37 (4.2%)	4 (2.5%)	41 (4.0%)
Asian	33 (3.8%)	6 (3.8%)	39 (3.8%)
Native American	16 (1.8%)	2 (1.3%)	18 (1.7%)
Other	7 (0.8%)	0	7 (0.7%)
Branch			
Army	721 (82.3%)	141 (89.8%)	862 (83.4%)
Air Force	13 (1.5%)	3 (1.9%)	16 (1.5%)
Navy	78 (8.9%)	6 (3.8%)	84 (8.1%)
Marines	34 (3.9%)	3 (1.9%)	37 (3.6%)
Coast Guard	0	0	0
National Guard	29 (3.3%)	4 (2.5%)	33 (3.2%)

RESULTS

Associations between Individual Exposures and Rank

The chi-square analyses showed that enlisted personnel were significantly more likely to have reported handling diesel or other petrochemical fuel, using insecticide cream, spending at least 12 hours outside per day, and experiencing physical reactions to sun exposure including sunburn, dizziness, light-headedness, muscle cramps, disorientation, and dehydration (Tables 5 and 6). Officers were more likely to have reported petroleum sprayed in their compound. There was no difference between officers and enlisted in the number of persons who experienced LOC while working in the sun, or reported exposure to oil well fires, lindane, insecticide spray, flea collars, or PB. Each OR was adjusted by gender but no significant difference was observed.

Table 5. Percentages and Odds Ratios of Chemical Exposures Reported by GW Veterans.

Exposure	Percentage of Enlisted Exposed	Percentage of Officers Exposed	Odds Ratio (95% CI*)
Petroleum sprayed	*28.2*	*38.6*	*0.63 (0.49, 0.84)***
Diesel handled	***68.4***	***41.3***	***3.07 (2.36, 4.00)*****
Proximity to oil well fire	25.4	24.5	1.05 (0.77, 1.42)
PB	46.4	46.7	0.99 (0.75, 1.31)
Lindane	3.8	3.1	1.23 (0.58, 2.59)
Insect cream	***51.7***	***44.2***	***1.35 (1.04, 1.76)***
Insect spray	47.4	48.2	0.97 (0.75, 1.27)
Flea collar	3.9	2.7	1.47 (0.67, 3.23)

Total (*n*) ranges from 1796 to 2066, with 1680 to 1950 enlisted and 225 to 264 officers.
*CI = Confidence interval
**Regular italics = Significant odds ratio less than 1
***Bold italics = Significant odds ratio greater than 1

Table 6. Percentages and Odds Ratios of Sun/Heat Exposure Symptoms Reported by GW Veterans.

Heat Illness Symptom	Percentage of Enlisted Exposed	Percentage Officers Exposed	Odds Ratios (95% CI)*
Sunburn	***10.6***	***2.3***	***4.97 (2.18, 11.32)****
Dizziness	***31.4***	***15.7***	***2.46 (1.74, 3.48)***
Light-headed	***45.0***	***24.6***	***2.51 (1.87, 3.37)***
Muscle cramps	***27.2***	***13.1***	***2.48 (1.70, 3.60)***
Disorientation	***9.8***	***3.1***	***3.43 (1.67, 7.04)***
Dehydration	***17.1***	***8.5***	***2.24 (1.42, 3.52)***
LOC	1.5	1.2	1.31 (0.40, 4.38)
Heat stress	***54.9***	***30.5***	***2.78 (2.10, 3.68)***
>12 Hours outside	***62.2***	***55.5***	***1.32 (1.01, 1.71)***

Total (*n*) ranges from to 2107 to 2174, with 1851 to 1915 enlisted and 256 to 261 officers
*CI = Confidence Interval
**Bold Italics = Significant odds ratio greater than 1

Next, contingency tables were made of case/control status versus the exposure variables, stratified by rank (Table 7). The case definition was met by 571 out of 1512 enlisted subjects (37.8%) and 45 out of 232 officers (19.4%). Every exposure variable was significantly related to being a case for enlisted subjects, but only *diesel handled* and *heat stress* variables were significant for officers. The rank-adjusted OR (Mantel-Haenszel) was significant for every variable except *flea collar.*

As shown in Table 7, the 95% CI's for officer OR's are wider than the CI's for the enlisted OR's. This reflects the smaller sample size of the officer group. However, officer sample size should have been adequate to demonstrate an effect as large as that seen in the enlisted group for most of the exposures. For example, 62.4% of enlisted cases reported completion of at least 1 pack of PB, compared to 42.1% of enlisted controls. The OR then for enlisted is 2.28 (95%CI=1.81, 2.87). More subjects were excluded from the PB chi-square calculation due to missing data than for any other exposure, leaving the officer sample size at 199. Completion of at least 1 pack of PB was reported by 48.5% of officer cases versus 49.1% of officer controls, which gives an OR of 0.96 (95% CI=0.46, 2.04). A sample the size of the officer group has 80% power to detect a difference as large as that seen in the enlisted group.

Table 7. Percentages and Odds Ratios of Exposures Reported by GW Veterans with and without Unexplained Symptoms

Exposure	**Percentage**		**Odds Ratios**
	Cases	**Controls**	**(95% Confidence Interval)**
Petroleum sprayed	***Enlisted: 43.3***	***22.2***	***Enlisted: 2.67 (2.08, 3.42)****
	Officers: 43.2	37.8	Officers: 1.25 (0.61, 2.58)
			Rank-adjusted: 2.46 (1.94, 3.10) **
Diesel handled	***Enlisted: 76.2***	***64.2***	***Enlisted: 1.78 (1.41, 2.25)***
	Officers: 57.8	*38.8*	*Officers: 2.14 (1.10, 4.14)****
			Rank-adjusted: 1.82 (1.46, 2.27)
Proximity to oil well fire	***Enlisted: 29.6***	***22.9***	***Enlisted: 1.41 (1.11, 1.80***
	Officers: 29.5	24.3	Officers: 1.31 (0.63, 2.71)
			Rank-adjusted: 1.401 (1.11, 1.76)
PB	***Enlisted: 62.4***	***42.1***	***Enlisted: 2.28 (1.81, 2.87)***
	Officers: 48.5	49.1	Officers: 0.96 (0.46, 2.04)
			Rank-adjusted: 2.12 (1.70, 2.63)
Lindane	***Enlisted: 6.9***	***2.5***	***Enlisted: 2.67 (1.53, 4.66)***
	Officers: 6.4	2.2	Officers: 3.27 (0.71, 15.20)
			Rank-adjusted: 2.72 (1.61, 4.61)

Table 7 continued.

Insect cream	***Enlisted: 65.2*** Officers: 56.8	***48.3*** 43.3	***Enlisted: 2.01 (1.61, 2.51)*** Officers: 1.72 (0.89, 3.35) **Rank adjusted: 1.98 (1.60, 2.44)**
Insect spray	***Enlisted: 63.3*** Officers: 61.4	***41.8*** 47.8	***Enlisted: 2.41 (1.93, 3.00)*** Officers: 1.74 (0.89, 3.41) **Rank-adjusted: 2.33 (1.89, 2.88)**
Flea collar	***Enlisted: 5.1*** Officers: 2.3	***3.0*** 2.1	***Enlisted: 1.72 (1.01, 2.93)*** Officers: 1.06 (0.12, 9.76) **Rank-adjusted: 1.67 (1.00, 2.80)**
Heat stress	***Enlisted: 76.7*** *Officers: 55.8*	***40.2*** *23.9*	***Enlisted: 4.91 (3.87, 6.22)*** *Officers: 4.02 (2.02, 8.02)* **Rank-adjusted: 4.82 (3.85, 6.03)**
>12 Hours outside	***Enlisted: 71.9*** Officers: 62.2	***61.9*** 55.4	***Enlisted: 1.58 (1.26, 1.97)*** Officers: 1.32 (0.68, 2.59) **Rank-adjusted: 1.55 (1.25, 1.92)**

Enlisted *n* ranges from 1264 to 1510, with 455 to 571 cases and 803 to 940 non-cases.

Officers *n* ranges from 199 to 232, with 33 to 45 cases and 164 to 187 non-cases.

*Bold italics = Significant enlisted odds ratio greater than 1

**Bold, regular type = Significant Mantel Haenszel pooled odds ratio greater than 1

***Regular italics = Significant officer odds ratio greater than 1

The Number of Exposures as a Risk Factor- ANOVA

Table 8 presents the one-way ANOVA results evaluating the total number of chemical exposure variables in relation to rank and case/control status. When the sum of chemical exposures was used as the dependent variable, the mean number of exposures was observed to be similar for both officer and enlisted control groups at 2.52 (95% CI=2.25, 2.79) and 2.49 (95% CI=2.36, 2.63) respectively. The analogous values for officer and enlisted case groups were 3.15 (95% CI=2.66, 3.63) and 3.43 (95% CI=2.70, 3.62). The difference between the groups was significant at the p<0.0001 level with an F statistic of 24.15.

Table 8. Mean Number of Chemical Exposures in Enlisted and Officer GW Veterans with and without Unexplained Symptoms.

	N	Mean # Exposures*	95% CI ** Lower Bound	95% CI Upper Bound
Officer controls	132	2.52	2.25	2.79
Enlisted controls	582	2.49	2.36	2.63
Officer cases	27	3.15	2.66	3.63
Enlisted cases	322	3.43	2.70	3.62

*Total possible exposures = 8

**CI = Confidence interval

Tukey HSD demonstrated that the difference between the groups was significant for case/control status but not significant for enlisted/officer status. The mean difference between the enlisted case group and both enlisted and officer control groups is significant at the p<0.001 level (Table 9). The difference between the officer case group and the 2 control groups did not reach statistical significance. However, as shown in Table 8, the 95% CI's for the 2 case groups were nearly identical, as were the CI's for the 2 control groups.

Table 9. Mean Differences in Total Number of Chemical Exposures between Enlisted and Officer Cases and Controls

Study Group Pair	Mean Difference (95% Confidence Interval)	Tukey HSD Adjusted p-value
Enlisted cases/Enlisted controls	0.94 (0.64, 1.23)	<0.001
Enlisted cases/Officer cases	0.28 (-0.56, 1.13)	0.83
Enlisted cases/Officer controls	0.91 (0.47, 1.35)	<0.001
Officer cases/Officer controls	0.63 (-0.27, 1.52)	0.27
Officer cases/Enlisted controls	0.65 (-0.18, 1.49)	0.18
Enlisted controls/Officer controls	-0.028 (-0.44, 0.38)	1.00

Logistic Regression

When case/control status was regressed on rank, the odds of being a case was 2.69 times higher in enlisted compared to officers (95% CI=1.74, 4.16) (Table 10). After adding the 8 chemical exposure variables to the model, the OR for rank remained virtually unchanged at 2.68 (95% CI=1.69, 4.24) (Table 11). With extremely non-significant exposures removed from the model (insecticide cream and flea collar), the OR was 2.66 (95% CI=1.70, 4.17).

When the *heat stress* variable was added to the model, the rank OR decreased to 2.06 (95% CI= 1.27, 3.32) (Table 12). After non-significant exposures were removed (insecticide cream, insecticide spray, and flea collar), the OR became 2.10 (95% CI=1.27, 3.24). It is likely that insecticide cream became insignificant when heat stress was added because insects were more prevalent when ambient temperatures were the highest. After exclusion of subjects with missing data, the regression analyses included 130 officer controls, 27 officer cases, 562 enlisted controls, and 314 enlisted cases.

Table 10. Odds of Reporting Unexplained Symptoms for Enlisted Relative to Officer GW Veterans.

Variable	Odds Ratio (95% Confidence Interval)	p-value
Rank	*2.69 (1.74, 4.16)*	*<0.001*

Table 11. Odds of Reporting Unexplained Symptoms for Enlisted Relative to Officer GW Veterans, Controlling for Self-reported Chemical Exposures during Deployment.

Variable	All Exposures		Fitted Model	
	OR (95% CI*)	p-value	OR (95% CI)	p-value
Rank	*2.68 (1.69, 4.24)*	*<0.001*	*2.66 (1.70, 4.17)*	*<0.001*
PB	1.24 (1.09, 1.40)	0.001	1.64 (1.24, 2.18)	<0.001
Insecticide cream	0.95 (0.67, 1.32)	0.742	Removed	
Insecticide spray	1.37 (0.98, 1.92)	0.068	1.35 (1.02, 1.80)	0.038
Flea collar	1.17 (0.50, 2.71)	0.720	Removed	
Proximity to oil well fire	1.17 (1.01. 1.36)	0.040	1.34 (0.99, 1.83)	0.059
Petroleum sprayed	1.70 (1.27, 2.29)	<0.001	1.67 (1.25, 2.23)	<0.001
Diesel handled	1.50 (1.10, 2.06)	0.011	1.54 (1.14, 2.09)	0.006
Lindane	2.35 (1.19, 4.67)	0.014	2.30 (1.17, 4.54)	0.016

*CI = Confidence interval

Table 12. Odds of Reporting Unexplained Symptoms in Enlisted Relative to Officer GW Veterans, Controlling for Self-reported Chemical Exposures and Sun/Heat Exposure.

Risk Factor	All Exposures		Fitted Model	
	OR (95% CI*)	p-value	OR (95% CI)	p-value
Rank	*2.06 (1.27, 3.32)*	*0.003*	*2.10 (1.27, 3.24)*	*0.002*
Chemicals				
PB	1.18 (1.03, 1.35)	0.016	1.54 (1.15, 2.04)	0.009
Insecticide cream	0.88 (0.62, 1.25)	0.473	Removed	
Insecticide spray	1.12 (0.78, 1.60)	0.551	Removed	
Flea collar	1.12 (0.45, 2.78)	0.807	Removed	
Proximity to oil well fire	1.11 (0.94, 1.30)	0.221	1.33 (0.95, 1.82)	0.097
Petroleum	1.58 (1.15, 2.17)	0.005	1.69 (1.25, 2.28)	0.001
Diesel	1.37 (0.93, 1.91)	0.063	1.40 (1.02, 1.93)	0.038
Lindane	1.93 (0.91, 4.11)	0.087	2.20 (1.07, 4.51)	0.032
Heat stress	2.65 (2.19, 3.20)	<0.001	4.62 (3.44, 6.20)	<0.001

*CI = Confidence interval

DISCUSSION

Previous studies revealed an association between unexplained symptoms in GW veterans and enlisted rank (Fukuda et al, 1998; Nisenbaum et al, 2000; Spencer et al, 2001). In the current study, simple logistic regression found that enlisted GW veterans were 2.7 times more likely than officers to report unexplained symptoms. No change was observed in the OR of enlisted veterans relative to officers reporting unexplained symptoms when 8 chemical exposure variables were added to the logistic regression model. A decrease in the OR was observed when a *heat stress* variable measuring sun/heat overexposure was added. These results suggest that the higher prevalence of unexplained illness among enlisted GW veterans may be partially due to having had sun/heat exposure, but not related to having had more chemical exposures than officers. This is consistent with the 2001 study by Spencer et al, which found that unexplained symptoms were associated with heat stress, the psychological stress of combat, and having sought medical attention during the GW, but not associated with chemical exposures.

Even after adjusting for the chemical exposures and *heat stress*, enlisted GW veterans were still over twice as likely to report unexplained symptoms as officers. Psychosocial factors may explain some of this remaining difference. Low socioeconomic status is an independent risk factor for most civilian diseases, so this pattern should not be surprising (Lantz et al, 1998; Marmot and Wilkinson, 1999).

All chemical exposures examined in this study were found to be associated with unexplained symptoms among enlisted personnel when examined individually. However, previous research has shown that these exposures fail to remain in a multivariate model due to correlation (Iowa Persian Gulf Study Group, 1997; Spencer et al, 2001; Unwin et al, 1999). The current study demonstrates that most chemical exposures studied singularly have a stronger association with unexplained symptoms among enlisted personnel than among officers. This is particularly remarkable for PB, which showed no association with unexplained symptoms in officers, but over a two-fold increase in cases among enlisted personnel who reported completing at least 1 pack. A possible mechanism for this observation could be an interaction between PB and stress (Friedman et al, 1996; Kaufer et al, 1998).

The ANOVA results from this study reveal that the total number of chemical exposures may be associated with unexplained symptoms, but are not associated with officer or enlisted status. Both enlisted and officers reporting unexplained symptoms also reported a higher number of chemical exposures. Although the difference between cases and controls was statistically significant only for enlisted, the officer data is still noteworthy. The officer case group had less power than the enlisted case group due to smaller sample size. The 95% CI's for the enlisted and officer case groups were almost identical, as were the 95% CI's of the enlisted and officer control groups. However, it should be noted that the chemical exposures totaled for ANOVA is neither an inclusive nor an exclusive list of potential toxins that GW veterans had been exposed to. Exposures such as DU and vaccines were not included due to poor reliability, and petrochemicals were counted as 2 separate exposure variables, personally handled by the veteran and sprayed in the compound. In addition, these results could be influenced by correlation between the exposures.

The data used in this study was originally collected to screen potential candidates for other research projects which subsequently included clinical exams and more intensive questioning. Using data collected for another purpose led to some challenges and limitations. Of the total 2222 subjects, 1189 (53.5%) had to be excluded from the logistic regression because of missing data. Many symptoms were not available in the current data set, which probably resulted in some cases being misclassified as controls. However, these misclassifications should have resulted in a bias toward the null hypothesis.

This study was based on self-reported data collected years after exposure, and significant overreporting of exposures among GW veterans has been demonstrated (McCauley et al, 1998). Research has likewise shown that symptoms that are self-reported on survey questionnaires are frequently not confirmed on subsequent clinical exam (McCauley et al, 1998). The dependent variable, *case/control* status, and an independent variable, *heat stress*, are both measured by self-reported symptoms. Subjects prone to somatization due to anxiety and/or depression may have involuntarily amplified symptoms (Barskey, 1995). Another measure of sun/heat exposure, the *>12 hours outside* variable, showed a much more modest strength of association with unexplained symptoms than the *heat stress* variable. However, the number of hours spent outside does not say anything about the amount of strenuous labor done while outdoors or whether the subject was in the sun or in the shade. Both factors would influence susceptibility of the soldier to heat-related illness.

Psychiatric illness also makes individuals more likely to suffer from heat-related illness (Barrow and Clark, 1998). This phenomenon cannot be attributed to somatization or psychotropic medication. Therefore, mental illness may cause unexplained symptoms indirectly through heat stress or may be a confounder.

Regardless, if the multisymptom illness reported by GW veterans is a post-combat syndrome caused by the multiple physical and psychological stresses of war, as suggested by Jones et al in 2002, then sun/heat overexposure is likely to be a contributing physical stressor. Heat stress due to high ambient temperature or fever is known to denature protein (De Maio, 1999). These damaged proteins are repaired by isoenzymes of heme oxygenase known as heat shock proteins, which also respond to protein damage caused by various chemicals and biological pathogens. An inadequate response by heat shock proteins in some individuals, perhaps due to genetic deficiency, is a plausible mechanism by which a variety of wartime chemical and physiological stressors, especially heat, may provoke a variety of symptoms. Because some biological pathogens are known inducers of heat shock proteins, this hypothesis is consistent with Da Costa's Civil War observation that the onset of "irritable heart syndrome" often followed an infectious disease (Hyams et al, 1996). Heme oxygenase deficiency has been postulated as an explanation for multiple chemical sensitivity syndrome (Morton, 2004), which has clinical similarities to UI in GW veterans (Miller, 1994;Morton, 1999; Ziem, 1992; Ziem, 1994), and is consistent with the ANOVA results of this study.

Therefore, it would be prudent to focus attention on the prevention of heat illness among soldiers deployed to SW Asia for the war on terrorism. In the current study, enlisted subjects were 2.8 times more likely than officers to report at least 1 symptom of sun or heat overexposure during deployment. Adjusting for rank, enlisted and officers combined who reported sun/heat overexposure were 4.8 times more likely to report unexplained symptoms. This study underscores the importance of adherence to the heat category guidelines used by the US military, which regulate work/rest cycles and clothing using the wet bulb global temperature (WBGT).

Heat illness often includes electrolyte abnormalities (Auerbach, 1989). Therefore, it is plausible that an episode of electrolyte imbalance may play a role in the etiology of chronic unexplained symptoms. The MRE (meal-ready-to-eat) is manufactured to provide balanced nutritional needs, including electrolyte replacement. The palatability of MRE's has improved since the first PGW, which should help to increase consumption during deployment. The troops should be educated about the importance of meals, just as they are instructed in the importance of adequate water intake. Sufficient time for meals should be given, as the mission allows. Further research on unexplained symptoms in GW veterans should include dietary questions, such as the number of MRE's and percentage of each MRE consumed daily.

Further research is also recommended to determine the role of psychosocial factors in the association between rank and unexplained symptoms in GW veterans. The series of logistic regression analyses could be repeated, examining changes in the OR of *rank* when psychosocial variables are added to the model. These variables could include combat stress as well as home stresses such as recent move, divorce, change of civilian job, etc. Additional research should also include a medical records review to confirm a history of heat-related illness such as heat cramps, heat exhaustion, or heat stroke.

SUMMARY AND CONCLUSIONS

The major findings of this study are:

1.) When examined singularly, most chemical exposures are more strongly associated with unexplained symptoms among enlisted GW veterans than among officers;

2.) The total number of chemical exposures is not associated with enlisted or officer status, but may be associated with unexplained symptoms among both enlisted personnel and officers;

3.) The higher incidence of chronic unexplained symptoms among the enlisted population cannot be attributed to chemical exposures, but may be partially due to a greater vulnerability to heat-related illness.

Attention should be paid to reducing heat-related illness among deployed military personnel in SW Asia through adequate water and food intake and adherence to the WBGT heat category guidelines. Further research using medical records to confirm a history of heat-related illness, and including psychosocial variables, is recommended.

REFERENCES

Auerbach P. (1995). Wilderness Medicine. St. Louis: Mosby-Year Book, Inc.

Barrow MW, Clark AK. (1998). Heat-related illnesses. American Family Physician. 58(3):749-759

Barsky A. (1995). Somatization Disorders. Presentation to the IOM Committee to Review Health Consequences of Service During the Persian Gulf War, Washington, D.C., May 1995.

Bourdette DN, McCauley LA, Barkhuizen A, Johnston W, Wynn M, Joos SK, Storzbach D, Shuell T, Sticker D. (2001). Symptom factor analysis, clinical findings, and functional status in a population-based case control study of Gulf War unexplained illness. Journal of Occupational and Environmental Medicine 43:1026-1040.

Corpus Christi Caller Times website. Accessed March, 2004. http://www.caller2.com/autoconv/newsworld99/newsworld119.html

DeFraites RF, Wanat ER, Norwood AE, Williams S, Cowan D, Callahan T. (1992). Investigation of a suspected outbreak of an unknown disease among veterans of Operation Desert Shield/Storm, 123d Army Reserve Command, Fort Benjamin Harrison, IN. Washington, D.C.: Walter Reed Army Institute of Research.

Deployment Health Clinical Center (DHCC) website. Accessed September, 2003. http://www.deploymenthealth.mil/clinicians/ccep.asp#1

Deploymentlink website. Accessed May, 2004. www.deploymentlink.osd.mil/deploy/prep/deploy_immun.shtml

De Maio, A. (1999). Heat shock proteins: Facts, thoughts, and dreams. Shock 11(1):1-12.

Engel CC, Engel AL, Campbell SJ, McFall ME, Russo J, Katon W. (1993). Posttraumatic stress disorder symptoms and precombat sexual and physical abuse in Desert Storm veterans. Journal of Nervous and Mental Disease 181:683-688.

Friedman A, Kaufer D, Shemer J, Hendler I, Soreq H, Tur-Kaspa I. (1996). Pyridostigmine brain penetration under stress enhances neuronal excitability and induces early immediate transcriptional response. Natural Medicine 2:1382-1385

Imperato A, Puglisi-Allegra S, Casolini P, Angellucci L. (1991). Changes in brain dopamine and acetylcholine release during and following stress are independent of the pituitary-adrenocortical axis. Brain Research 538:111-117.

Fukuda K, Nisenbaum R, Stewart G, Thompson W, Robin L, Washko R, Noah DL, Barrett DH, Randall B, Herwaldt BL, Mawle AC, Reeves WC. (1998). Chronic multisymptom illness affecting Air Force veterans of the Gulf War. Journal of the American Medical Association 280:981-988.

Gulflink, website of the office of the Special Assistant for Gulf War Illnesses. Accessed April, 2004. http://www.gulflink.osd.mil/

Haley RW, Hom J, Roland RS, Bryan WW, Van Ness PC, Bonte FJ, Devous MD, Mathews D, Fleckenstein JL, Wians FH, Wolfe GI, Kurt TL. (1997). Evaluation of neurologic function in Gulf War veterans: A blinded case-control study. Journal of the American Medical Association 277:223-230.

Haley RW, Kurt TL. (1997). Self-reported exposure to neurotoxic chemical combinations in the Gulf War: A cross-sectional epidemiologic study. Journal of the American Medical Association 277: 231-237.

Haley RW, Billecke S, La Du BN. (1999). Association of low PON1 type Q (type A) arylesterase activity with neurologic symptom complexes in Gulf War veterans. Toxicology & Applied Pharmacology 157:227-33.

Haley RW, Fleckenstein JL, Marshall WW, McDonald GG, Kramer GL, Petty F. (2000). Effect of Basal Ganglia Injury on Central Dopamine Activity in Gulf War Syndrome. Archives of Neurology 57:1280-1285.

Hom J, Haley RW, Kurt TL. (1997). Neuropsychological correlates of Gulf War syndrome. Archives of Clinical Neuropsychology 12:531-544.

Hyams KC, Wignall FS, Roswell R. (1996). War syndromes and their evaluation: From the US Civil War to the Persian Gulf War. Annals of Internal Medicine 125:395-405.

Hyams KC, Riddle J, Trump DH, Graham JT. (2001). Endemic infectious diseases and biological warfare during the Gulf War: A decade of analysis and final concerns. American Journal of Tropical Medicine and Hygiene 65(5):664-70.

Institute of Medicine. (1996). Health Consequences of Service during the Persian Gulf War: Recommendations for Research and Information Systems. Washington DC: National Academy Press.

Iowa Persian Gulf Study Group. (1997). Self-reported illness and health status among Gulf War veterans: a population-based study. Journal of the American Medical Association. 277:238-245.

Jones E, Hodgins-Vermaas R, McCartney L, Everitt B, Beech C, Poynter D, Palmer I, Hyams K, Wessely S. (2002). Post-combat syndromes from the Boer War to the Gulf War: A cluster analysis of their nature and attribution. British Medical Journal 324(7333):321-4.

Kaufer K, Friedman A, Seidman S, Soreq H. (1998). Acute stress facilitates long-lasting changes in cholinergic gene expression. Nature 393:373-377.

Lantz PM, House JS, Lepkowski JM, Williams DR, Mero RP, Chen J. (1998). Socioeconomic factors, health behaviors, and mortality. Journal of the American Medical Association 279:1703-1708.

Marmot M, Wilkinson R (Eds.) (1999). Social Determinants of Health. Oxford: Oxford University Press.

McCauley LA, Joos SK, Lasarev MR, Storzbach D, Bourdette, DN. (1999). Gulf War Unexplained Illnesses: Persistence and Unexplained Nature of Self-Reported Symptoms. (1999). Environmental Research 81:215-223.

McCauley LA, Joos SK, Spencer, PS, Lasarev, M, Shuell T, Members of the Portland Envronmental Hazards Research Center. (1999). Environmental Research 81: 195-205.

McCauley LA, Rischitelli G, Lambert WE, Lasarev M, Sticker DL, Spencer PS. (2001). Symptoms of Gulf War veterans possibly exposed to organophosphate chemical warfare agents at Khamisiyah, Iraq. International Journal of Occupational and Environmental Health 7:79-89.

McCauley LA, Lasarev M, Sticker D, Rischitelli MD, Spencer PS. (2002). Illness experience of Gulf War veterans possibly exposed to chemical warfare agents. American Journal of Preventive Medicine 23:200-206.

Miller CS. (1994). Multiple chemical sensitivity and the Gulf War veterans. Presentation to NIH Technology Assessment Workshop Panel on the Persian Gulf Experience and Health, Bethesda, MD. April, 1994.

Morton WE. (1999). Multiple chemical sensitivity (MCS) and the possibility of chemical-induced porphyrinopathy as explanation for a proportion of Gulf War veteran illness. For use at Conference on the Health Impact of Chemical Exposures during the Gulf War. Atlanta, GA, February 1999.

Morton WE. (2004). Heme Oxygenase Deficiency: Another Candidate for Possible Explanation of the Pathogenesis of Multiple Chemical Sensitivity (MCS). (Unpublished).

Nathanson CA. (1975). Illness and the feminine role: A theoretical review. Social Science and Medicine 9:57-62.

Nathanson CA. (1980). Social roles and health status among women: the significance of employment. Social Science and Medicine 14A:463-471.

Nisenbaum R, Drue BH, Reyes M, Reeves W. (2000). Deployment Stressors and a chronic multisymptom illness among Gulf War veterans. Journal of Nervous and Mental Diseases 188:259-266.

Organization for Prohibition of Chemical Weapons (OPCW), ICA division website. Accessed November, 1999. http://www.opcw.nl/chemhazlnerve.htm

Perconte ST, Wilson AT, Pontius EB, Dietrick AL, Spiro KJ. (1993). Psychological and war stress symptoms among deployed and non-deployed reservists following Persian Gulf War. Military Medicine 158:516-521.

Presidential Advisory Committee on Gulf War Veterans' Illnesses. (1996). Final Report. Washington DC: US Government Printing Office.

Rook GA, Zunla, A. (1997). Gulf War syndrome: is it due to a systemic shift in cytokine balance towards a Th2 profile? The Lancet 349:1831-1833.

Spencer PS, McCauley LA, Lapidus JA, Lasarev M, Joos SK, Storzbach, D. (2001). Self-reported exposures and their association with unexplained illness in a population-based case-control study of Gulf War veterans. Journal of Occupational and Environmental Medicine 43:1041-1056.

Sutker PB, Davis JM, Uddo M, Ditta SR. (1995). Assessment of psychological distress in Persian Gulf troops: Ethnicity and gender comparisons. Journal of Personality Assessment 64:415-427.

US Army Medical Research Institute of Chemical Defense website. Accessed November, 1999. http://chemdef.apgea.army.mil/chemcasu/NervAgnt.htm#OVERVIEW

Unwin C, Blatchley N, Coker W, Ferry S, Hotopf M, Hull L, Ismail K, Palmer I, David A, Wessely S. (1999). Health of UK servicemen who served in Persian Gulf War. Lancet 353:169-178

VA website. Accessed May, 2003. www.va.gov/health/environ/faq.htm

Waitzkin H, Waterman B. (1974). The Exploitation of Illness is Capitalist Society. Indianapolis: The Bobbs-Merrill Educational Publishing Co.

Wolfe J, Brown PJ, Kelley JM. (1993). Reassessing war stress: Exposure and the Persian Gulf War. Journal of Social Issues 49:15-31

Wolfe J, Proctor S, Sullivan M, Duncan-Davis J. (1995). Posttraumatic stress and physical health: Does gender play a role? Poster presentation, Harvard Medical School.

Ziem GE. (1992). Multiple chemical sensitivity: Treatment and follow-up with avoidance and control of chemical exposures. Toxicology and Industrial Health 8:73-86.

Ziem GE. (1994). Public meeting presentation to the Committee to Review the Health Consequences of Service During the Persian Gulf War. IOM, Washington, DC, February 1994.