



A Guide to Gulf War Veterans' Health

Independent Study Course
1997, Revised: June 2001
Released: March 2002

Sponsored by
Department of Veterans Affairs
Employee Education System



This is a Veterans Health Administration System-wide Training program, sponsored by the Employee Education System in cooperation with the Office of Public Health and Environmental Hazards, Department of Veterans Affairs. It is produced by the Employee Education System.



DEPARTMENT OF VETERANS AFFAIRS
UNDER SECRETARY FOR HEALTH
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MESSAGE FROM THE UNDER SECRETARY FOR HEALTH

I am very pleased to introduce this Department of Veterans Affairs Veterans Health Initiative continuing medical education independent self-study program on Gulf War Veterans Health Issues.

This program represents a complete revision of a course prepared in late 1997 and released in March 1998. A great deal has happened during the intervening four years. Indeed, a total of 192 federally-sponsored research efforts have now been authorized. The help we enlisted of the National Academy of Sciences' Institute of Medicine has enabled us to better understand the problems of Gulf War veterans. Interagency and international cooperation has improved. Centers for the Study of War-Related Illnesses are being established. Thousands of additional Gulf War veterans have sought and received medical care from VA. Education and outreach efforts have been enhanced and disability compensation has been provided to more veterans.

Importantly, because we have been listening carefully to Gulf War veterans, we have learned more about their health problems and concerns.

Despite our focused approach, care of Gulf War veterans has remained challenging. The wide array of environmental exposures encountered by the brave men and women who served in the Gulf War and their possible adverse health effects; the many and diverse symptoms and conditions reported; and the presence of unexplained symptoms and undiagnosed illnesses in some veterans have been frustrating to some veterans, families, and clinicians.

This continuing medical education self-study program is designed to provide basic information to clinical personnel about the problems and concerns of Gulf War veterans and to provide current information about VA's program to help these veterans.

We hope that this text will assist those who care for Gulf War veterans to provide the best possible health care to these veterans. They have earned no less!

A handwritten signature in blue ink that reads "Thomas L. Garthwaite".

Thomas L. Garthwaite, M.D.
Under Secretary for Health



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Independent Study Outline

Background: This independent study module is being released as a part of the Veterans Health Initiative (VHI). The VHI is a comprehensive program of continuing education that recognizes the connection between certain health effects and military service, and emphasizes better military medical histories for veteran patients in order to provide them with the best available care.

Purpose: This independent study is designed to provide an introduction to issues regarding Gulf War veterans' health. It represents a complete revision of the independent study released in March 1998. The revised independent study provides an overview of the Gulf War experience, the Department of Veterans Affairs and the Department of Defense health programs available for Gulf War veterans, and the common symptoms and diagnoses of these veterans. Emphasis is placed on providing the most recent information from clinical and scientific studies of Gulf War veterans' illnesses.

Objectives: After completing this independent study, participants will be able to:

- recognize the most common symptoms and diagnoses of Gulf War veterans,
- describe current programs established by the Department of Defense and the Department of Veterans Affairs on behalf of Gulf War participants, and
- discuss recent research studies and findings that relate to the health concerns of Gulf War veterans.

Outcome: The expected outcomes of this independent study are improved sensitivity to the effect of military experiences and exposures on veteran patients' health and attitudes, improved patient satisfaction, increased awareness of the occupational risks in a patient's history and a data base for future research activities.



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Content Materials:

- The Health Impact of Service in the Gulf War
- Gulf War Health Care
- VA Gulf War Registry Health Examination Program/Department of Defense Comprehensive Clinical Evaluation Program
- Other VA and DoD Health Care Programs: Centers for the Study of War-Related Illnesses; DoD's Centers for Deployment Health; DoD's OSAGWI and the Office of the Special Assistant to the Under Secretary of Defense (Personnel And Readiness) for Gulf War Illnesses and Medical Readiness and Military Deployments
- Spouses and Children Examination Program
- Large-Scale Clinical Trials and the ALS Study
- Clinical Practice Guidelines: Unexplained Symptoms
- Clinical Risk Communication: Explaining Casualty Risk to Gulf War Veterans With Multisymptom Illnesses
- Studies of Gulf War Veterans' Mortality, Morbidity and Reproductive Health
- Mortality Among U.S. and U.K. Gulf War Veterans
- Morbidity Studies Among Gulf War Veterans
- Medically Unexplained Symptom-Based Illnesses Among Gulf War Veterans
- Reproductive Health Among Gulf War Veterans
- Health Risk Factors
- Pesticides
- Chemical and Biological Warfare Agents
- Vaccinations and Pretreatments
- Depleted Uranium
- Infectious Diseases
- Disability Compensation and Undiagnosed Illnesses
- Outreach and Education for Gulf War Veterans and VA Employees
- Supplemental Reading and Additional References



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CHAPTER 1 THE HEALTH IMPACT OF SERVICE IN THE GULF WAR

Approximately 697,000 men and women served in Operations Desert Shield and Desert Storm from August 1990 to June 1991. The Americans who served in the Gulf War were unique. Compared to any force in U.S. history, there was more ethnic diversity and more women, parents and activated members of the Reserves and National Guard who were temporarily uprooted from their civilian lives.

Iraqi forces suffered significant casualties during the Gulf War, but the Coalition forces led by the U.S. quickly accomplished their mission of liberating Kuwait, while sustaining remarkably few combat casualties. The extraordinarily low casualty rate among U.S. service members during the war was a clear military health triumph. Before the war, many had expected thousands or even tens of thousands of U.S. casualties. In fact, casualty rates in this quick and decisive war were less than one-tenth of one percent of the 697,000 U.S. troops deployed between August 2 and the cease-fire.

Rates of non-battle injuries and diseases also were remarkably low compared to earlier military engagements involving U.S. service members. This public health success can be attributed to early preventive medicine efforts, minimal contact with local populations and virtually no consumption of alcohol. Nevertheless, as reports emerged in 1992 and 1993 of increasing health problems among Gulf War veterans, it was clear that the government needed a comprehensive response to this emerging health issue. Immediate answers to veterans' health concerns were not forthcoming, and many veterans blamed the federal government for not doing enough to respond.

This *Guide to Gulf War Veterans' Health* is an update of an earlier study guide published in 1998. Comparison of this edition to the earlier one is striking because it underscores how rapidly our understanding of the issue has expanded and evolved during this period. In the earlier guide, there were so few scientific studies on the Gulf War and health that it was practical to review and abstract most of them. In the present 2002 Guide, the section on research alone has more than 115 references — an enormous increase!





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The range of mortality and morbidity studies of Gulf War veterans available today form a solid basis for reaching conclusions about the health impact of service in the Gulf War.

Perhaps the greatest progress in our understanding of the Gulf War and health is the appreciation that some deployment-related illnesses appear to be an inevitable consequence of deployment itself. With that realization comes an appreciation of the need and the responsibility for improving our ability to diagnose and treat patients with such conditions, and to provide the appropriate and relevant training for health care providers who must respond. To that end, in April 2001, VA announced the establishment of two new Centers for the Study of War-Related Illnesses, with the goal of serving not just for Gulf War veterans, but all veterans of past and future combat and peace-keeping missions.

Gulf War Deployment

Although combat casualties during the war were remarkably low, nevertheless, living conditions for U.S. service members in the Gulf War region were far from hospitable. Operations Desert Storm and Desert Shield were quickly over, but for many U.S. service members, the war meant being stationed for months in isolation in a bleak desert environment.

Initially, numbers of deployed U.S. service members were dwarfed by the large and apparently battle-hardened Iraqi forces, who were known to possess and to have used chemical weapons in the past against their enemies. No one knew that the war would be over so quickly, and deployed U.S. service members suffered uncertainty about when they might return home. During preparations for war, they had few amenities and lived under arduous and austere conditions that were not always conducive to good health. The weather, initially extremely hot and humid, changed to cold and damp by the time the war actually began.

U.S. service members generally found themselves housed in crowded warehouses, a few local buildings and tents. Available living quarters allowed for little privacy. Prepackaged meals were their principal diet and local produce and goods were quickly put off-limits for health reasons. Sanitation was far from ideal, and latrines and communal washing facilities were the norm. In some areas, desert filth flies were everywhere.

U.S. service members also were exposed to a wide range of hazardous materials. Not surprisingly, following the war, many veterans had concerns about the health impacts of these exposures and living conditions.



Early Health Problems

Within months of returning home from the Gulf War in 1991, some veterans from the United States, Great Britain and Canada began to report a variety of symptoms such as fatigue, headache, joint pains, sleep disturbances and memory problems. These diverse symptoms became seen by some as a unique health problem, which became the subject of controversy and extensive research efforts. Although it has been more than 10 years since the war and much more is now understood about the consequences of service in the Gulf War, many questions remain about the nature of the health problems experienced by some Gulf War veterans.

Since 1992, about 130,000 of the 750,000 Gulf War veterans from the U.S., Great Britain and Canada have received a systematic clinical registry examination conducted by the U.S. Departments of Veterans Affairs (VA) and Defense (DoD), or comparable examination programs in other countries. Many evaluated veterans were found to be ill with a wide range of disorders, but a unique or previously unidentified syndrome has not been identified. Examination of family members of veterans in other studies also has not found an indication of a unique health problem, although more data are still forthcoming.

Symptom-Based Illnesses

Most Gulf War veterans who come to VA for health care or to participate in the VA health registry receive conventional diagnoses and treatments. Most have health problems similar to those experienced by veterans of other eras. However, some veterans report chronic multi-symptom illnesses that often are difficult to diagnose. Thus, most of the symptoms reported by veterans in VA registry examinations were found to be caused by conventional illnesses. However, in about 20 percent of examinations, primary diagnoses of physical complaints could not be provided. (For comparison, approximately 17 percent of Vietnam veterans on VA's Agent Orange registry examination have undiagnosed symptoms).

Drawing conclusions about the health of the average Gulf War veteran from the VA registry is not practical because registry participants in the VA registry are self-selected, and there is no control group with which to compare health outcomes. To overcome these limitations and to reliably evaluate the health of the *entire* Gulf War veteran population, VA initiated a population-based epidemiological study called the National Health Survey of Gulf War Era Veterans and Their Families. This is a cross-sectional, health-outcomes survey of a true population-based sample of 15,000 U.S. service members and 15,000 era veterans. Published results show that in comparison with Gulf War-era veterans who did not serve in the theater of operations, Gulf War veterans report higher prevalence of functional impairment, health care utilization, symptoms and medical conditions, and a higher rate of low general health



perception. Gulf War veterans also report greater rates of adverse reproductive health outcomes — self-reported data that is currently being validated through examination of medical records. As described in Chapter 3, other studies of reproductive outcomes have not shown increased rates.

Other epidemiological studies on sub-groups of Gulf War veterans (e.g., veterans from Iowa, veterans from a specific unit, etc.) also consistently find that veterans report many diverse symptoms and illnesses at higher rates compared to control groups. But studies by both VA and others also find that Gulf War veterans do not show unexpected differences in mortality rates or rates of hospitalizations compared to era veterans.

Outside Evaluations

Since 1993, six expert panels in the United States, both within and outside of the government, have evaluated available clinical and research data on Gulf War health issues. These panels have been unable to identify a unique Gulf War syndrome or to find any specific wartime exposures to be a significant cause of illness among veterans. Additional scientific panels, such as the National Academy of Sciences, are continuing to evaluate Gulf War health questions.

Health care providers, researchers and expert review panels have been unable to confirm any unique Gulf War illness. In fact, the term “Gulf War Illness” is misleading because it implies that some single, unique illness has been found in this group. Nevertheless, a variety of studies clearly demonstrate that some Gulf War veterans suffer from a range of difficult-to-diagnose health problems. The unexplained illnesses reported by some Gulf War veterans are remarkably similar to other recognized, symptom-based conditions, including chronic fatigue syndrome (CFS) and fibromyalgia. These sometimes debilitating conditions also are a significant health problem in the general U.S. population, and in other populations, as well. In general, such conditions are characterized by multiple symptoms involving multiple organ systems and are not consistently associated with any objective physical signs or laboratory abnormalities.

Research Problems

Designing and conducting research studies into the nature and causes of illnesses among Gulf War veterans has been hampered by the lack of a reliable “case-definition” of a unique Gulf War veteran illness, and by the absence of accurate exposure information. Although a specific case definition is elusive, some researchers have developed “working” case-definitions of possible war-related illnesses for study purposes. For example, in an epidemiological study of deployed Air Force personnel, the CDC defined a chronic, multi-symptom illness similar to CFS.



In the CDC study, 47 percent of Gulf War veteran Air Force personnel examined fulfilled the CDC diagnostic criteria, but so did 15 percent of non-deployed U.S. civilian subjects. Strikingly, cases in Gulf War veterans did not cluster by time, duration or location of deployment, by military occupational specialty or by direct participation in combat. A similar epidemiological study of British Gulf War veterans reported similar results. A study of Kansas veterans reported Gulf War veterans who fought and served in Iraq or Kuwait were more likely to report symptoms compared to veterans who served primarily on shipboard during the war. Although the frequency of symptom reporting was higher among British Gulf War veterans, similar symptoms were found among a cohort of non-deployed military personnel and a cohort of veterans sent more recently to the Bosnia conflict.

VA and other departments and agencies are continuing to collaboratively evaluate possible causes of veterans' health problems. More than \$155 million has been allocated for 192 research initiatives on this subject. While some of these projects have been completed and published, most of the research studies are ongoing. Mortality and morbidity studies of Gulf War veterans completed under this program are described in Chapter 3 of this Guide.

Factor analysis also has been used by a number of researchers as a possible new tool for investigating the nature of Gulf War veterans' illnesses. This is a statistical technique developed for reducing data, developing scales and for identifying relationships among multiple variables. In a variety of studies including active duty Navy Seabees, veterans from Iowa, the U.K., and Air Force studies, both Gulf War veterans and non-deployed era veterans report similar groups or patterns of self-reported symptoms, although at different rates. The identification of the similar, if not identical, patterns of symptoms among both deployed and non-deployed military personnel and civilians in these studies suggest that the health complaints of Gulf War veterans are likely to be similar to those found in the general military and civilian populations. The value of factor analysis, as a means of investigating Gulf War veterans' health, compared to more conventional clinical assessments, remains to be demonstrated.

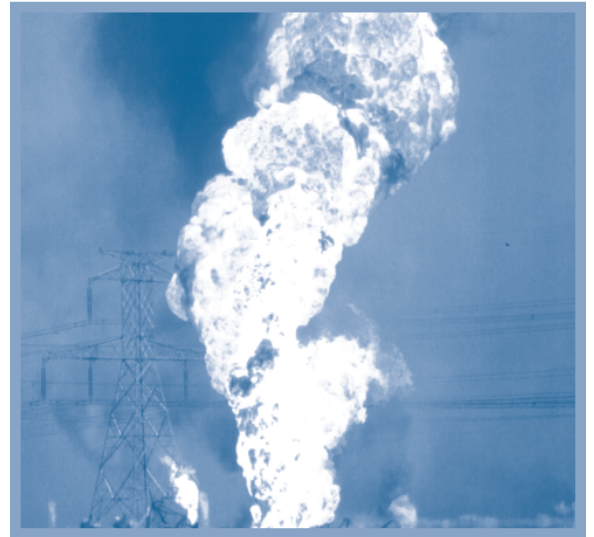
Health Impacts of Military Deployments

Review of historical reports of health problems following previous U.S. military engagements may help us to understand current Gulf War veterans' health issues. In fact, poorly understood "war syndromes" characterized by multiple physical symptoms have been reported since at least the U.S. Civil War. Consistent with this observation, unexplained syndromes have been reported among troops involved in more recent hazardous military deployments to the Balkans and other areas around the world. Unexplained illnesses appear to be one inevitable health consequence associated with any hazardous military or peace-keeping deployment.



Ongoing Review of Gulf War Health Effects

The health impact of service in the Gulf War continues to be the focus of numerous conferences, review boards and committees. Perhaps most significant is the ongoing National Academy of Sciences' Institute of Medicine (IOM) comprehensive review and analysis of scientific and medical literature on the health effects associated with selected Gulf War environmental exposures. The mandate for these IOM reviews was established in Public Law 105-368. It is modeled after the IOM review process established by the Agent Orange Act of 1991 for Vietnam veterans exposed to Agent Orange. The initial IOM report, released on September 7, 2000, focused on the possible adverse health effects of exposure to depleted uranium, the chemical warfare agent sarin, vaccinations against botulinum toxin and anthrax, and pyridostigmine bromide. That report concluded that either these risk factors were unlikely to be associated or there was insufficient data to conclude there was any association with Gulf War veterans' illnesses at the levels of exposures likely experienced by veterans during the war. Additional potential health hazards are being evaluated in ongoing IOM studies.



Summary

Considerable progress has been made in evaluating and treating illnesses among Gulf War veterans and in determining the prevalence of symptoms. Most Gulf War veterans are healthy today and have successfully readjusted to post-war life, or they have diagnosable health problems. VA has been able to respond to the complexity of veterans' health problems; most are readily diagnosed and effective treatments are available. Nevertheless, some veterans continue to report symptoms that cannot be easily diagnosed and may be debilitating.

Although nearly all symptoms examined are found to be more prevalent among Gulf War veterans, the clustering of symptoms is not unique in this group. Some difficult to diagnose illnesses among Gulf War veterans are very similar to conditions commonly diagnosed in the general population. Evidence-based approaches have found useful treatments for certain chronic symptom-based illnesses such as CFS and fibromyalgia. To this end, VA, in collaboration with DoD, is preparing clinical practice guidelines to assist VA health care practitioners who are treating veterans with these complaints.



The initiation of clinical practice guidelines is supported by the July 2001 IOM report, *Gulf War Veterans: Treating Symptoms and Syndromes*, which concluded that the undiagnosed symptoms reported by some Gulf War veterans correspond closely to symptoms of unknown origin or cause experienced by many non-veteran Americans. Those symptom-based illnesses significantly overlap with the following seven common diagnoses:

1. fibromyalgia (joint pain, sleep disturbances, fatigue),
2. chronic fatigue syndrome (fatigue, headache, cognitive dysfunction),
3. depression (fatigue, loss of memory and other general symptoms, cognitive dysfunction, and sleep disturbances),
4. irritable bowel syndrome (diarrhea and other GI symptoms, abdominal pain, nausea and vomiting),
5. headache,
6. Post Traumatic Stress Disorder (PTSD), and
7. panic disorder.

Encouragingly, the IOM identified many scientific reports of effective treatment for persons with these seven diagnoses. These treatments may provide a basis of effective treatments for veterans with undiagnosed illnesses, including CFS and fibromyalgia.

With thousands of ill Gulf War veterans and so many potential causes, VA, in concert with other Federal departments and agencies, has developed a comprehensive program to respond to this situation. Succeeding chapters in this Guide describes our health care surveillance and medical treatment initiatives for veterans of the Gulf War.

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CHAPTER 2 GULF WAR HEALTH CARE

2A. VA Gulf War Registry Health Examination Program and Department of Defense Comprehensive Clinical Evaluation Program

VA Program

Even before the 1991 Gulf War cease-fire, VA medical care personnel became concerned about potential health problems of U.S. service members resulting from exposure to clouds of smoke from oil well fires. In response, VA developed a clinical registry called the VA Gulf War Registry Health Examination to help the department evaluate any health problems and to provide better health care for returning U.S. service members. Officially authorized by Congress on November 4, 1992, by the "Persian Gulf War Veterans Health Status Act," all Gulf War veterans are eligible for participation in the Registry.

VA's Gulf War Registry Health Examination Program provides all Gulf War veterans the opportunity to receive a systematic medical examination and appropriate baseline laboratory tests at VA medical centers located across the Nation. Additionally, a complete medical history is obtained and documented in the veteran's medical records. Supporting this comprehensive health program, each VA medical center has an assigned Registry Coordinator and a Registry Physician. As of January 2000, about 1,137,000 military personnel (including those deployed as part of Operations Desert Shield and Desert Storm, as well as post-conflict veterans from the ongoing U.S. military presence after the 1991 cease-fire), have been deployed to the Persian Gulf region. About 852,000 veterans have separated from military service and become eligible for VA health care, as well as the Registry Examination. National Guard and National Reserve personnel also are eligible.

As of September 2001, more than 82,000 Gulf War veterans have responded to VA's outreach efforts that encourage participation in this free examination program. More than 2,600 veterans who served in the Gulf region after the war (from July 31, 1991, until the present) also have been evaluated. This centralized clinical database also allows VA to communicate with veterans and provides a mechanism to catalogue prominent symptoms, reported exposures and diagnoses.

The registry is only one component of clinical care for Gulf War veterans; VA maintains an extensive national health care program that provides both inpatient and outpatient clinical care. As of October 1, 2000, 33,990 Gulf War veterans have been seen as inpatients at VA facilities, and 346,584 Gulf War veterans have been seen as outpatients at VA facilities. There is some overlap between these two numbers.



By law, the Gulf War Veterans Health Registry also lists each individual U.S. service member who served in the Gulf War and 1) applies for VA health care, 2) files a compensation claim relative to service in the Gulf War, 3) dies and is survived by a spouse, child or parent who files a claim for dependency and indemnity compensation based on Gulf War service, 4) requests the Gulf War Health Registry Examination, or 5) receives from the Department of Defense (DoD) a health examination similar to the VA examination and who requests inclusion in VA's registry. Currently, more than 250,000 veterans are included on this consolidated roster. VA uses this combined roster for outreach to Gulf War veterans. In July 1998, VA significantly expanded the Registry Examination to include a new seven page depleted uranium (DU) questionnaire and to offer analysis of a 24-hour urine collection for measuring uranium levels for any Gulf War veteran who is concerned about possible DU exposure.

DoD Program

In 1994, DoD began a similar health registry for Gulf War veterans who are still on active duty called the Comprehensive Clinical Evaluation Program (CCEP). The CCEP provides a systematic and uniform medical evaluation for active duty personnel and also for their family members. As of January 1, 1999, there have been 36,684 military personnel evaluated in the CCEP. It provides a two-phase clinical evaluation supervised by a board-certified physician. All participants were provided a Phase I examination. For those without current medical problems or who had health problems that could be satisfactorily explained, no additional evaluation was conducted.

If referral consultations and specialized tests were clinically indicated, participants proceeded to Phase II examination at a DoD regional medical center. Patients with unexplained symptoms, or symptoms not completely explained by the second phase diagnoses, were often referred to the Specialized Care Program at Walter Reed Army Medical Center. This additional referral is sometimes called "Phase III."

Findings of VA's Gulf War Registry Exam

The Registry is in essence a case series. Participants are self-selected, there is no comparison (control) group and exposures are self-reported and generally impossible to validate. These limitations make it difficult to establish valid conclusions about the health of Gulf War veterans as a whole. However, the large numbers of individuals examined and the systematic examination process provide important clinical insight into the variety of illnesses suffered by Gulf War veterans and a source of hypotheses for future research. Moreover, any widespread serious physiologic disease should have been detected in this very large patient series.



Registry data do not appear to support the concern that Gulf War veterans are experiencing any new diseases, but the data is less useful for evaluating if veterans are suffering from specific diagnoses or symptoms at higher rates than expected. That analysis requires other types of epidemiological studies. In fact, through the work of the Persian Gulf Veterans Coordinating Board (and its successor, the Military and Veterans Health Coordinating Board) Research Working Group, there are many federally-sponsored epidemiological studies now underway to help us compare the rates that Gulf War veterans are suffering from specific medical problems, compared to control groups (see Chapter 3).

Review of the 1999 VA revised registry data indicate that many participants are “well” when they are evaluated. While 74 percent of evaluated veterans report their health status as “all right,” “good” or “very good,” the remaining 26 percent report “poor” or “very poor” health.

TABLE 1
MOST FREQUENT COMPLAINTS AMONG THE 19,721 VETERANS ON THE
REVISED PERSIAN GULF REGISTRY¹

Complaints	Frequency	Percent²
Loss of memory and other general symptoms	5,794	29.4
Headache	5,204	26.4
Fatigue	4,639	23.5
Skin rash	4,574	23.2
Muscle/joint pain	4,096	20.8
Sleep disturbances	2,553	12.9
Diarrhea and other GI symptoms	2,352	11.9
Shortness of breath	2,050	10.4
Chest pain	1,041	5.3
Choking sensitivity	939	4.8
Abdominal pain	916	4.6
Other symptoms involving skin and integumentary tissue	692	3.5
Cough	676	3.4
No complaint	1,527	7.7

¹ Data as of February 1999, prepared by VA Environmental Epidemiology Service.

² Percent of 19,721 veterans.



As shown on Table 1, the most common symptoms reported by Gulf War veterans are (in decreasing frequency): 1) loss of memory, 2) headache, 3) fatigue, 4) skin rash, 5) muscle/joint pain, 6) sleep disturbances, 7) diarrhea and other gastrointestinal symptoms, and 8) shortness of breath.

TABLE 2
DISTRIBUTION OF DIAGNOSES FOR THE 19,721 VETERANS ON THE REVISED PERSIAN GULF REGISTRY¹

Diagnosis	Number	Percent
Musculoskeletal and connective tissue	7,286	36.9
Mental disorders	6,887	34.9
Skin and subcutaneous tissue	3,813	19.3
Respiratory system	3,626	18.4
Digestive system	3,451	17.5
Nervous system	3,441	17.4
Circulatory system	2,083	10.6
Injury and poisoning	2,020	10.2
Infectious diseases	1,785	9.1
Genitourinary system	1,126	5.7
Neoplasm (malignant)	149	0.8
No medical diagnosis	4,664	23.6

¹Data as of February 1999, prepared by VA Environmental Epidemiology Service.

Table 2 shows that the most common primary diagnoses for this group are diverse and related to the following: 1) musculoskeletal and connective tissue conditions, 2) mental disorders, 3) respiratory conditions, 4) skin and subcutaneous conditions, 5) digestive conditions, and 6) nervous system conditions. Approximately 24 percent of this group received no medical diagnosis. In that group, the most common complaints are 1) headache, 2) loss of memory, 3) fatigue, 4) skin rash, 5) muscle/joint pain, 6) sleep disturbances, 7) diarrhea and other GI, and 8) shortness of breath.

Records of VA inpatient and outpatient diagnoses for Gulf War veterans show a similar diagnostic picture to veterans on the Gulf War Health Registry. With outpatients, the most



common diagnoses are 1) diseases of the musculoskeletal system, 2) symptoms, signs and ill-defined conditions, 3) diseases of the nervous system, and 4) mental disorders. With inpatients the most common diagnoses are 1) mental disorders, 2) symptoms, signs and ill-defined conditions, 3) diseases of the digestive system, and 5) diseases of the musculoskeletal system.

The VA registry provides little information about the relative severity of the diagnosed and undiagnosed symptoms reported by Gulf War veterans. Nevertheless, some information is available that sheds light on the severity of these conditions. (For example, Gulf War veterans have filed more than 240,000 claims with VA.) The most common claim is for impairment of the knee, followed by 2) skeletal system disability, 3) back strain, and 4) arthritis due to trauma. About 11,400 (4.7 percent) of these claims are for undiagnosed illnesses; a new compensation claim category established by Congress, in 1994. These claims represent a wide range of conditions. The most common relate to 1) musculoskeletal disease, followed by 2) miscellaneous neurological, 3) systemic disease, and 4) lower digestive system.

Findings from DoD's CCEP

Results from DoD's CCEP closely mirror those from VA's Registry Examination. In April 1996, about 20,000 Gulf War veterans had completed CCEP. The three most common primary diagnoses were "diseases of the musculoskeletal system and connective tissue" (18.6 percent), "mental disorders" (18.3 percent), and "symptoms, signs, and ill-defined conditions" (17.8 percent). Nine percent of participants were found to be "healthy," without a clinically significant new illness. Among the 3,558 participants with a primary diagnosis of "symptoms, signs, and ill-defined conditions," no single ICD-9-CM subcategory predominated, and such veterans had a wide variety of symptoms, with fatigue, headache, memory problems and sleep disturbances being the most frequent presenting complaints. A relatively large percentage of CCEP participants had a psychological condition as either a primary (18 percent) or secondary (18 percent) diagnosis.

Among CCEP participants, examinations revealed the following diagnoses: connective tissue disease as either a primary or secondary diagnosis (74 participants); disorders of immunity (five with selective immunoglobulin A immunodeficiency and one with selective immunoglobulin M immunodeficiency); skin cancer (9), lymphoma/leukemia (22), other types of cancers (30); glomerulonephritis (13) and renal insufficiency (12); interstitial pulmonary fibrosis (14); and polyneuropathy (8) or peripheral neuropathy (34). Common skin infections accounted for 60 percent of primary infectious disease diagnoses. A common or distinctive organic pathology was not identified among over 800 veterans with neuromuscular symptoms who had extensive neuropsychological evaluations.



The types of medical conditions that would result from postulated Gulf War environmental hazards were diagnosed infrequently, including: neurologic disease from possible chemical weapons or pesticide exposure, interstitial pulmonary disease from smoke or sand inhalation, renal disease from heavy metal exposure and immunologic dysfunction from various combinations of exposures. Participants frequently reported all surveyed exposures including: exposure to diesel and other fuels (88 percent); use of pyridostigmine bromide pills (74 percent); exposure to oil well fire smoke (71 percent); personal use of insect repellents (66 percent); anthrax (49 percent) and botulinum (26 percent) vaccinations; and observing combat casualties (57 percent) or actual combat (38 percent).

Researchers reviewing 18,495 DoD registry records concluded that the latency of symptom reporting (often more than one year after the war), combined with the poor correlation with any self-reported wartime exposures, fail to clearly link any specific exposure with postwar symptom reporting. Similarly, review of signs and symptoms in 145 VA registry participants referred for rheumatological evaluation found primarily nonspecific arthralgias, osteoarthritis and fibromyalgia. Similar studies of 457 Gulf War veterans evaluated for possible rheumatological conditions found a high prevalence of common conditions without any unique diagnosis or condition. Examination of the first 65 DoD registry patients seen for neurological symptoms found no consistent patterns of neurologic disease. Review of data from 12,744 DoD registry participants with principal or secondary diagnoses coded as ICD-9 “signs, symptoms and ill-defined conditions” found many diagnoses in this category represented a wide variety of common symptoms, with no evidence of any new or unique syndrome.

In contrast, pulmonary function testing with 48 VA Gulf War veteran participants referred for pulmonary medicine evaluation found a higher than expected midvital flow capacity, suggesting chronic inflammation of upper airways. Researchers speculated that these effects could be the chronic manifestations of exposure to smoke and/or other irritants from the Kuwaiti oil well fires during the war. Finally, clinical examination of 16 female Gulf War veterans found a high proportion with gynecological problems during and after service in the Gulf.

Undiagnosed or Difficult-to-Diagnose Illnesses

Most Gulf War veterans coming to the VA have commonly seen symptoms and clinical signs and are given conventional diagnoses and appropriate treatment. Although the prevalence of unexplained illnesses among all Gulf War veterans is uncertain, some veterans report more difficult to diagnose chronic symptoms including fatigue, memory loss or joint pain. Some researchers have grouped these symptoms as fatigue, neurocognitive and musculoskeletal. Some of these patients may respond to well-accepted symptomatic treatments, even though their physicians have not identified specific exposure agents or underlying illness. The wide



range of symptoms and conditions associated with difficult-to-diagnose conditions suggests that there may be no unifying etiology that could account for all unexplained illnesses.

Independent scientific medical and scientific expert groups also have been unable to identify any unique symptom complex or new illness that might constitute a unique syndrome. These include the 1996 report of the Presidential Advisory Committee on Gulf War Veterans' Illnesses, the 1996 report of the Institute of Medicine, the 1994 report of the National Institutes of Health, and the 1994 report of the Defense Science Board Task Force on Persian Gulf War Health Effects.

In response to those Gulf War veterans whose symptoms remain unexplained after initial examination, in 1993 the VA developed expanded assessment guidelines called the Uniform Case Assessment Protocol (UCAP). These clinical guidelines for evaluating ill-defined or unexplained illnesses suggest 22 additional tests and auxiliary specialty consultations, and outline supplementary diagnostic procedures based on the specific symptoms of the veteran and the clinical judgment of the registry physician. An "unexplained illness" is defined as one or more symptoms, generally without objective clinical findings, which do not conform to a characteristic clinical presentation allowing for a diagnosis, but which appear to be causing a decline in the veteran's functional status or quality of life. The UCAP clinical guidelines are also used by DoD. VA, in collaboration with DoD, currently is working on developing clinical guidelines that include effective diagnoses and treatments for chronic fatigue syndrome and fibromyalgia, which may be highly relevant for this group of patients.

VA has responded to the problem of undiagnosed illnesses in Gulf War veterans in other ways, as well. In 1998, VA solicited proposals from VA clinicians to initiate new demonstration projects for testing new and innovative approaches to treating and improving the patient satisfaction of Gulf War veterans who suffer from undiagnosed and ill-defined disabilities. Five two-year projects were selected at the following VA medical centers: Brockton/West Roxbury (Boston), MA; Portland/Seattle, OR; Tampa, FL; Birmingham, AL; and Cincinnati/Cleveland, OH. Reports from these five projects are available at <http://www.va.gov/health/enviro/DemoProj/Overview.htm>.

Recently, VA announced the establishment of two new VA Centers for the Study of War-Related Illnesses that, in part, will address this difficult medical issue. Additional information about the Centers can be found in the following subchapter.



2B. Other VA and DoD Health Care Programs: Centers for the Study of War-Related Illnesses; DoD's Centers for Deployment Health; DoD's OSAGWI and the Office of the Special Assistant to the Under Secretary of Defense (Personnel And Readiness) for Gulf War Illnesses, Medical Readiness and Military Deployment

The health problems reported by the majority of veterans who enroll in VA's registry health examination program are effectively diagnosed and appropriately treated. However, for those Gulf War veterans with debilitating symptoms that remain unexplained after completing the Uniform Case Assessment Protocol, following consultation with a referral center physician, their local VA physician may refer them to one of VA's four regional Gulf War Referral Centers at: 1) Washington, DC; 2) Houston, Texas; 3) West Los Angeles, California; and 4) Birmingham, Alabama. With more extensive assessment permitted by hospitalization, most of these veterans have been diagnosed as having well-recognized illnesses. As of September 2001, about 771 veterans have been evaluated at one of the four VA referral centers.

The successful clinical role these centers have played with Gulf War veterans with disabling but difficult-to-diagnose illnesses, in part has led to the recognition of the need for such clinical care for veterans returning from other combat and peacekeeping missions.

Centers for the Study of War-Related Illnesses

Congress, veterans, veteran service organizations and others have demanded that we develop better ways of responding to the health needs of all American veterans. Public Law 105-368 directed VA to contract with the Institute of Medicine (IOM) to help develop a plan for establishing national centers for the study of war-related illnesses and post deployment health issues. In a November 1999 report, an IOM Committee concluded that creating Centers for the Study of War-Related Illnesses (CSWRI), similar in structure to VA's Geriatric Research, Education and Clinical Centers (GRECCs), "should contribute greatly to the advancement of knowledge in this area," and recommended that VA proceed. VA sent out request for proposals for two CSWRIs to be selected through a competitive peer-review process. These called for four major program components to focus on veteran health issues, including research, risk communication, clinical care and education. Each CSWRI was required to be located at a VA medical facility or facilities having strong academic affiliations with medical and other health professional schools. They also were requested to actively collaborate with the DoD, as appropriate.



In May 2001, VA announced two new CSWRI at VA Medical Centers at East Orange, NJ, and Washington, DC. Initially, the CSWRI will be established with approximately \$2 million per site, plus up to \$250 thousand for up to five pilot research projects. After two years, they are expected to have 10 to 12 FTE at each CSWRI. Program evaluation and oversight is through the Office of Public Health and Environmental Hazards, and also will involve a VA headquarters Steering Committee. The centers also will work closely with the Office of Research and Development.

The current Gulf War Referral Centers will be phased out as the Centers for the Study of War-Related Illnesses (CSWRIs), described below, become fully operational. In this regard, the CSWRIs are expected to fulfill the clinical role the Referral Centers provided for Gulf War veterans in addition to a broader audience of veterans.

DoD's Centers for Deployment Health

The Department of Defense has established three centers to help veterans by protecting their health and that of their service members, now and in the future. To accomplish this objective, DoD has created a new center, converted an existing clinical center and continued to support a third center.

Specifically, DoD has redesignated the Naval Health Research Center in San Diego as the DoD Deployment Health Research Center. The mission of this center includes epidemiological studies investigating the longitudinal health experience of previously deployed military personnel, and the development and evaluation of appropriate health surveillance strategies.

The Gulf War Health Center, located at Walter Reed Army Medical Center in Washington, DC, was converted to the DoD Deployment Health Clinical Center. Its mission includes responsibility to 1) maintain and improve primary and tertiary health care for individuals with deployment-related health care (e.g., the Comprehensive Clinical Evaluation Program and Specialized Care Program); 2) maintain, improve and explore the use of health information systems to improve the military continuum of deployment-related health care and to improve military medicine's capacity for early identification of emerging deployment-related illnesses; 3) develop a program of military-relevant clinical research to include multi-center clinical trials, risk communication strategies and clinical health services research, and 4) assist in developing, implementing and sustaining an evidence-based military medical deployment health education program to increase the volume, quality, rate and ease of clinically-relevant research knowledge disseminated to military health care providers regarding deployment-related health care.



The Specialized Care Program at Walter Reed is an intensive treatment program designed to address persistent, disabling symptoms among Gulf War veterans. It features three weeks of multidisciplinary treatment of patients in small groups of three to eight individuals. The program is based upon internationally recognized centers for management of chronic illness. It provides state-of-the-art care for those suffering from multiple symptoms such as fatigue, joint pain, headache, skin rash, digestive problems, weight gain or loss, and memory problems.

The third center, the Defense Medical Surveillance System (DMSS), continues to serve as the tri-service medical surveillance system. The DMSS, an executive information system whose data base contains current and historical data on diseases and medical events, and longitudinal data on personnel and deployments, provides access to the necessary before, during, and post-deployment data to conduct DoD-wide surveillance and research.

DoD's OSAGWI and the Office of the Special Assistant to the Under Secretary of Defense (Personnel and Readiness) for Gulf War Illnesses, Medical Readiness and Military Deployment

On November 12, 1996, Dr. John White, Deputy Secretary of Defense, directed the establishment of the Office of the Special Assistant to the Deputy Secretary for Gulf War Illnesses (OSAGWI). That office, during the next four years, operated under a three-part mission: 1) Gulf War veterans will receive appropriate medical care; 2) DoD will do everything possible to understand and explain Gulf War illnesses; and 3) DoD will put in place all required military doctrine, personnel, medical policies and procedures to minimize any future problems from exposure to biological and chemical warfare agents and other environmental hazards.

OSAGWI conducted a number of investigations, held town meetings, established a website (www.gulflink.osd.mil) and newsletter (GulfNEWS), and produced a large volume of publications. In fact, in just four years, OSAGWI produced 18 interim and six final case narratives, nine information papers, five interim and a final environmental exposure report, and four closeout reports. The RAND Corporation, under contract to OSAGWI, published five reports reviewing the medical and scientific literature on the known health effects of substances to which Gulf War veterans may have been exposed. Gulf War veterans and the American public have relied on these publications to answer many of the questions surrounding the unexplained illnesses of Gulf War veterans.

In April 2001, the new Deputy of Defense announced the establishment of the Office of the Special Assistant to the Under Secretary of Defense (Personnel and Readiness) for



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Gulf War Illnesses, Medical Readiness and Military Deployments, to replace OSAGWI. This redesignation reflects the efforts of the new administration to reorganize personnel and resources in a way that improves internal structure and communication.

They will continue the ongoing investigations and publish the findings on their GulfLINK website.



2C. Spouses and Children Examination Program

In November 1994, Congress enacted Public Law 103-446, "Veterans' Benefits Improvement Act of 1994." This legislation required VA to gather sufficient medical data relevant and appropriate to determine the nature and extent of any association between any illness or disorder of the spouse and child and the illness of the veteran.

VA implemented the VA Funded Examination Program for the Spouses and Children of Persian Gulf War Veterans to fulfill the legislative mandate in Public Law 103-446. Under this authority, VA could provide examinations to any individual who is the spouse or child of a veteran, is listed in the Persian Gulf War Veterans Registry established under Public Law 102-585, Section 702, and is suffering from illness or disorder; 2) is suffering from, or may have suffered from, an illness or disorder (including a birth defect, miscarriage or still-birth) which cannot be disassociated from the veteran's service in the Persian Gulf; and 3) has granted VA permission to include in the Registry relevant medical data from the examination.

Under the initial requirements of Public Law 103-446, the examination period was to terminate on September 30, 1996. Registration for the program began April 1, 1996. VA developed an examination protocol similar to that of the veterans who served in the Persian Gulf theater. In addition, VA initially identified 16 facilities across the country to act as coordinating facilities. These facilities were responsible for controlling all administrative aspects of the program in the field. Now there are 38 coordinating sites.

In October 1996, Congress extended the program under Public Law 104-262, the "Veterans Health Care and Eligibility Reform Act" to December 31, 1998. With the enactment of Public Law 105-368 "Veterans Program Enhancement Act," the program was expanded and extended through December 31, 1999.

In addition to the extension of the program, Public Law 105-368 provided for program improvements through "enhanced flexibility" by permitting examination to be completed under a fee arrangement. Due to the complexity involved in contracting for pediatric examinations and the great distance many spouses and children were traveling for examinations, VA is now allowing facilities the option of paying private providers to conduct the examinations. However, the veteran (or spouse) must still call the toll-free helpline (1-800-PGW-VETS; 1-800-749-8387) to register for the program and confirm their eligibility.



Results of exams are entered into a registry, which will ultimately be used for analysis and comparisons with illnesses reported by veterans who served in the Persian Gulf theater. With enactment of Public Law 106-117, the Veterans Millennium Health Care and Benefits Act in November 1999, the Gulf War Spouses and Children Examination Program has been extended through December 31, 2003. However, this program faces many of the limitations inherent in the registry program.

This program provides examinations only. VA medical treatment of any conditions diagnosed in spouses and children is **not** authorized under this program.



2D. Large-Scale Clinical Trials and the ALS Study

The Department of Veterans Affairs (VA) is leading an effort with the Department of Defense (DoD) to conduct two large-scale, randomized, controlled trials for the treatment of undiagnosed illnesses experienced by Gulf War veterans. In the spring of 1998, VA's Cooperative Studies Program initiated a nine-month planning effort for two treatment trials concentrating on 1) exercise-behavioral therapy (EBT), and 2) antibiotic treatment (ABT). These two studies offer the prospect of significantly advancing scientific knowledge of the unexplained illnesses affecting some Gulf War veterans and the ability to treat their related symptoms. Both of these studies have finished recruiting subjects and the experimental phases are substantially complete. Following analysis of the data, published results should be available by 2002.

Exercise-Behavioral Therapy (EBT) Trial

The EBT trial focuses on the use of aerobic exercise and cognitive behavioral therapy in an effort to provide comprehensive, coherent and effective treatments to veterans and active duty soldiers ill after their service in the Gulf War. The primary study objective is to assess whether aerobic exercise combined with cognitive behavioral therapy (CBT) will improve the physical functioning of ill patients, and whether the combination of exercise and CBT will be more beneficial than either therapy alone. Additional study objectives include evaluation of any improvements in the cardinal symptoms of Gulf War illnesses, especially pain, fatigue and cognitive difficulties. The ability to decrease the level of disease-related distress and improve emotional functioning of persons with Gulf War illnesses also will be evaluated. There are four treatment groups as patients are allocated to receive both aerobic exercise and CBT together, either treatment individually, or usual and customary care.

One or more of these proposed treatment interventions are currently employed for patients ill with such conditions as Chronic Fatigue Syndrome, fibromyalgia, arthritis and back pain, headaches and irritable bowel syndrome. The CBT intervention is not a singular approach to all the patient's problems. Rather, it is a set of techniques that can be tailored for specific problems or illnesses. The techniques are used to produce cognitive change and are based largely on the development of problem solving skills. Unlike a drug, physical manipulation or surgery where the patient is the passive recipient of a given treatment, CBT works best when the patients take an active role in the management of their symptoms. A growing body of research supports the idea that patient behavior and patient thinking can improve some illnesses to the same or greater degree than traditional medical approaches. CBT cannot "cure" Gulf War veterans' illnesses, but may help Gulf War veterans better manage their symptoms and improve their quality of life.



Antibiotic Treatment (ABT) Trial

The ABT trial focuses on a hypothesized infectious cause for the variety of symptoms experienced by Gulf War veterans. The primary hypothesis of the study is that antibiotic treatment directed against a species of *Mycoplasma* will improve the functional status of patients with Gulf War illnesses who are tested as *Mycoplasma* positive at baseline. *Mycoplasmas* are the smallest free-living infectious agents. They are distinct from viruses because of their ability to grow in cell-free media, and from bacteria because they lack a cell wall and the ability to synthesize cell wall precursors. Although there is no established, definitive link between infection with this organism and Gulf War veterans' illnesses, undetermined numbers of ill veterans are taking the antibiotic Doxycycline for as long as one year in hopes of improving their health. In addition, there are anecdotal reports that this tetracycline has been useful in ameliorating the symptoms of Gulf War veterans.

A putative infectious etiology for Gulf War veterans' illnesses provides an attractive hypothesis because antibiotics could possibly cure these patients' symptoms. Unfortunately, anecdotal reports do not establish treatment benefit and a rigorous trial is necessary to address the question definitively. Accordingly, the ABT trial's primary hypotheses is to determine whether a 12-month course of antibiotic treatment (Doxycycline) directed against *Mycoplasma* species will improve the functional status of patients with Gulf War veterans' illnesses who are tested as *Mycoplasma* positive. The study also will determine whether antibiotic treatment reduces symptoms including pain, fatigue, and neuro-cognitive difficulties, converts *Mycoplasma* positive patients to a *Mycoplasma* negative status, and whether the treatment benefit persists beyond one year. To be enrolled in this trial, patients must have tested positive for the presence of *Mycoplasma* genetic material and fit the above symptom categories.

ALS Study

Amyotrophic lateral sclerosis (ALS or Lou Gehrig's disease) is a fatal neurodegenerative disease that destroys the brain and spinal cord nerve cells that control muscle movement. As the brain and spinal cord motor nerve cells die, muscles weaken and shrink, and rapid, severe paralysis occurs. Some veterans have raised concerns about a possible association between ALS and service in the conflict.

VA initiated a study in March 2000 designed to identify as completely as possible the total number of cases of ALS among Gulf War veterans and determine whether there is any relationship between the disease and service in the Gulf War. Researchers have completed identifying and recruiting the subjects for this study. They came from all veterans who were on active duty during the Gulf War — regardless of whether they served in the Gulf



War theater or elsewhere during the war, and who were diagnosed with a motor neuron disease. If researchers find an elevated risk for developing ALS among Gulf War veterans, the study results will have major implications for veterans, VA, and DoD. Such a study among a relatively young group of veterans also could provide new knowledge about the epidemiology and possible causes of ALS.

Based upon this study, VA and DoD researchers expect that they will have a better understanding of the rate of occurrence of ALS among Gulf War veterans. A panel of neurological experts is reviewing records and, if necessary, arranging physical examinations to confirm or rule out ALS among study participants. The full study will determine if ALS occurs at a higher-than-expected rate among Gulf War veterans.

Initially, clinicians at VA and DoD identified 28 patients with possible ALS among the 697,000 who were deployed to the Gulf region during the year after the August 1990 Desert Shield mobilization. A preliminary review of those cases and a review of a national mortality study of death rates in all Gulf War veterans indicated no unusual increase in the rate of ALS among Gulf War veterans and no excess deaths from ALS. The ALS Association (ALSA) estimates the prevalence of ALS in the United States at between six and eight cases per 100,000 persons.

A panel of experts from VA, DoD, the Department of Health and Human Services (HHS), the Centers for Disease Control and Prevention (CDC), the ALSA and university representatives recommended that VA develop a national epidemiologic study of ALS among Gulf War veterans. The study, directed by the Epidemiologic Research and Information Center at the Durham (NC) VA Medical Center, is a collaboration involving VA, DoD, HHS and the CDC. ALSA is advising the study leaders.



2E. Clinical Guidelines: Unexplained Symptoms

VA defines clinical guidelines as “recommendations for the performance or exclusion of specific procedures or services derived through a rigorous methodological approach that includes the following:

- determination of appropriate criteria, such as effectiveness, efficacy, population benefit, or patient satisfaction; and
- literature review to determine the strength of the evidence (based in part on study design) in relation to these criteria.”

VA has been active in the development and implementation of evidence-based guidelines, which make explicit links between practice recommendations and quality of supporting evidence. Guidelines enhance the management of a given condition, problem or patient population by identifying best-care practices.

A number of Gulf War veterans have complained about a wide variety of symptoms. Most of these symptoms have easily been explained and a diagnosis provided. However, some Gulf War veterans have medical problems that cannot be explained, even after extensive testing and consultations.

VA completed a draft clinical practice guideline on Chronic Fatigue Syndrome (CFS) and fibromyalgia (FM) in August 2001, and anticipates that guidelines will be implemented soon thereafter. For availability, check the VA website at www.va.gov/gulfwar. The goal of this guideline is to give clinicians the tools they need to consider diagnoses and treatments for CFS and fibromyalgia. These two symptom-based illnesses appear to be similar or related to the problems reported by some Gulf War veterans with difficult-to-diagnose illnesses. Although clinical guidelines are typically developed through a consensus process, there is no current consensus for the conditions noted above. Nevertheless, the researchers and clinicians involved in developing guidelines for CFS and fibromyalgia have assembled an impressive collection of pharmacological and non-pharmacological intervention, with clinically-proven efficacy.



2F. Clinical Risk Communication: Explaining Causality to Gulf War Veterans with Chronic Multisymptom Illnesses¹

Nearly all Gulf War veterans recall a range of environmental and combat exposures during their Gulf War service. Frequently, veterans have developed their own theories and ideas about the extent that these exposures represent threats to their current and future health, theories that sometimes are causally related to the subsequent onset of symptoms, though very often they are not. Frequently, the veteran seems to overestimate or overvalue the apparently low chance that a rare, improbable cause (e.g., in theater vaccinations or biological weapons exposure) is responsible for symptoms than more ordinary and likely causes (e.g., early degenerative joint disease in an airborne infantry soldier). Under these circumstances, the manner and message of the physician when communicating may well subsequently alter the veteran's:

- acceptance of and adherence to the physician's medical advice and opinion regarding causation,
- satisfaction with care,
- confidence in the physician,
- future level of functioning, and
- likelihood of returning successfully to various life roles.

Much has been written about the doctor-patient relationship. One of the more commonly addressed issues is the skill with which physicians communicate unwelcomed information to patients. Probably more common for most physicians, however, is the need to effectively convey reassuring information when the available medical evaluation suggests the absence of a catastrophic or rapidly progressive problem.

There are several barriers when attempting to offer reassurance to patients. These include the lack of physician time, patient mistrust of their physicians, the limited ability of most patients and many clinicians to appreciate the impact of chance and probability on diagnosis and cause, the abstract or complex nature of many illnesses, and the deceptively difficult interpretation of diagnostic testing. Indeed, there is a large amount of literature suggesting that the diagnostic characteristics of various common clinical tests are even a source of confusion for most physicians, let alone for patients. The most important reason physicians have difficulty counseling many patients may be the growing public mistrust of the medical

¹Adapted from a presentation by Charles C. Engel, Jr., MD, MPH, at the Conference on Illnesses among Gulf War Veterans, June 1999, Washington, DC.



profession. This mistrust is amplified in clinical situations where the physician is perceived as having to balance the interests of the patient with the interests of a third-party payer, an employer or a social program.

Risk communication is the science of communicating information about risk under circumstances involving some combination of low trust, high concern, perceived crisis or differential interpersonal power. The National Research Council (NRC) Committee on Risk Perception and Communication defined risk communication more formally as, “An interactive process of exchange of information and opinion among individuals, groups and institutions. It involves multiple messages about the nature of risk and other messages, not strictly about risk, that express concerns, opinions, or reactions to risk messages or to legal and institutional arrangements for risk management.” Risk communication as a social science has developed out of the need to enhance bilateral communications about risk that occur regularly between organizations, governmental agencies, businesses or industries and the constituents, employees or other stakeholders who fear that such groups may unreasonably or unfairly jeopardize their health.

Nearly all clinicians regularly encounter patients under conditions of high concern, low trust, perceived crisis or differential interpersonal power. Clinicians can learn to improve their capacity for effective doctor-patient communication about risk, disease and prognosis from the burgeoning literature on risk communication. This brief overview, then, is an attempt to offer a risk communication perspective to inform and improve physicians' *clinical risk communication* skills. Improved clinical risk communication may alleviate unnecessary patient distress and physical health concern, and reduce frustration and tension in the doctor-patient relationship. Most importantly, it may help patients simplify the daunting task of understanding the relevant health risks and discarding irrelevant risks in the context of what is generally a brief health care encounter. The remainder of this paper borrows some points from the risk communication literature in an effort to construct a model for thinking about clinical communication of risk to ailing Gulf War veterans concerned about war-related exposures.

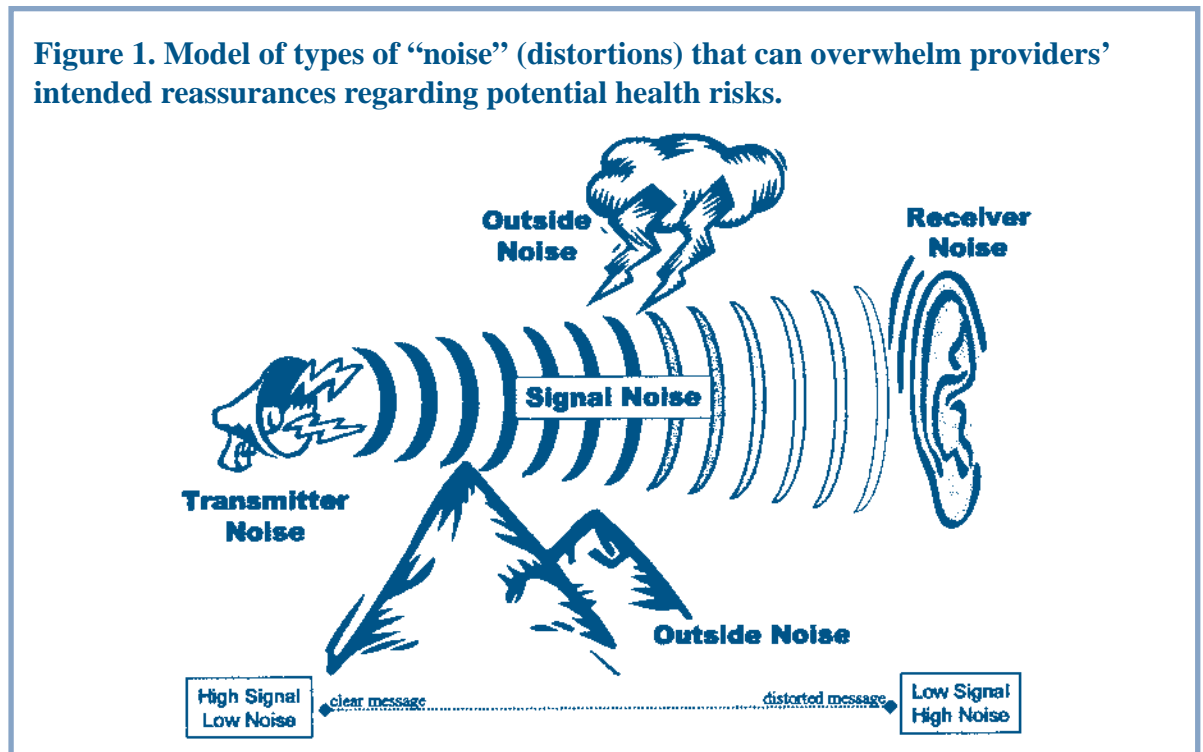
Modeling the Clinical Communication Encounter

Research literature convincingly shows that people (clinicians as well as patients) often misjudge causal mechanisms behind illnesses and events. In simple terms, most of the risks we worry about are probably not the risks that evidence suggests are most important. To understand this observation further, it is useful to consider some ways that miscommunication of risk occurs. Signal theory is one way to model the communication of information between doctor and patient (see Figure 1). A signal (the intended message regarding risk) emits from



a transmitter (e.g., the doctor) to a receiver (e.g., the patient). Any number of influences creates “noise” (distortion) that hinders the accurate reception and processing of the signal. Noise can come from the transmitter (the talker), the signal (the message), the receiver (the listener), or the outside (the context or environment).

Figure 1. Model of types of “noise” (distortions) that can overwhelm providers’ intended reassurances regarding potential health risks.



Transmitter Noise

Transmitter noise occurs when the person doing the speaking unwittingly clouds the verbal message with nonverbal and usually unintended messages that detract or distract from the verbal message. Commonly, the clinician is the transmitter, and there are many factors that relate to the way the clinician is perceived that determine the amount of noise sent with the intended message. Research has explored the factors that impact perceived risk and suggests that the single largest determinant is the extent that the person doing the talking is perceived as trustworthy. The extent that the person talking is perceived as empathic and caring is in turn the single largest determinant of whether a communicator is viewed as trustworthy. In medicine, most of us value scientific and technical competence as perhaps the hallmark of an excellent clinician. Common sense might well suggest to us that perceived communicator competence and expertise would be a more important factor than research suggests it is (see Figure 2).



The professionalization process in medicine sometimes promotes the image of physician as the detached and objective scientist over that of the warm and interpersonally-connected confidante. In contrast, clinicians interested in improving their communication skills should develop the capacity to present themselves as caring, empathic, honest and open.

Figure 2. Factors That Impact Perceived Trust and Credibility



Signal Noise

Signal noise is increased when some aspect of the message (for example, its wording, order or structure) creates misunderstanding. The structure of the message is particularly important. One simple method that has been suggested by risk communication experts is to use a structure that you can remember, using the following mnemonic: “**C**ompassion & **C**aring **D**etermines **R**isk **A**ceptability.” First, begin our message with a statement of **COMPASSION**. Second, offer a brief “sound-bite” **CONCLUSION**. Third, state no more than two pieces of supporting **DATA**. Fourth, **REPEAT** your conclusion. Last, describe the **ACTION** you intend to take in response to the situation.

For example, suppose a patient is seeing you for fatigue, diffuse pain and difficulty concentrating, and you have been unable to determine a clear medical etiology. During one visit, the patient finally says, “Look doc, several men in my unit have died from symptoms like this. The way I look at it, this has got to be something chemical from the War.” One response might be, “Mr. Smith, I have great respect for the way you are battling with your symptoms. I know this must be a frustrating and frightening time for you (compassion statement). I am confident that you are not dying (conclusion statement). Studies show that Gulf War veterans have poorer health than expected, though causes are often elusive. The good news is that death rates are not elevated in Gulf vets (data statements). I can assure you that you are not dying (repeat conclusion statement). So far, we have not found anything on testing, so I don’t recommend that we do more of it right now. I’d like to schedule you to see me in two weeks to see if things are better, worse or the same (action statement).”



The first and last components essentially frame your message, so be sure to include them. The step that veterans' are frequently most concerned about is *action*. Patients are much less sensitive about clinicians' opinions if they feel reassured that they are not going to be used to justify clinical inaction or, worse yet, rejection.

TABLE 3
FACTORS CONTRIBUTING TO DECREASED ACCEPTABILITY
OF A GIVEN HEALTH RISK.

Risks are generally less acceptable if perceived as:

- involuntary (e.g., pollution) rather than voluntary (e.g., smoking);
- man-made or industrial rather than natural;
- unfamiliar or novel rather than familiar;
- dreadful in their consequences;
- catastrophic, dramatic or memorable;
- unfair (some people benefit, while others suffer consequences);
- as subject to contradictory statements from responsible sources (worse yet, the same source). Dangerous to children, pregnant women, or future generations;
- mysterious, hidden or poorly understood;
- uncontrollable or inescapable;
- harming identifiable victims (rather than anonymous ones);
- irreversible or delayed harm;
- mistrusted party or source is responsible; and
- involving a passive response from a responsible party or source.

Bennett, P: Understanding responses to risk: some basic findings. Risk Communication and Public Health. P. Bennett and K. Calman, Editors. Oxford University Press, New York; 1999.

Receiver Noise

Receiver noise is the distortion introduced by factors related to or having an impact on the listener. Risk communication experts emphasize that peoples' responses to risk are seldom predicated on technical data. Instead, decisions about risk are value judgments. Just like informed consent, they are based upon highly personalized factors that may sometimes appear



irrational to the clinician-observer. As clinicians, it is generally not our place to make decisions for our patients. However, it is crucial that we are aware of the issues that can adversely effect our patients' decisions (strong emotions, including mistrust, worry, fear or outrage) so that we do not unnecessarily exacerbate them. Some of the most crucial factors that alter individuals' appraisal of risk are listed in Table 3.

It should be clear from Table 3 that sometimes what clinicians say or do can alter the extent that a patient's judgment about risk might become clouded. For example, it is almost always unwise to directly compare risks with patients. Comparing, say, the chance that a Gulf War veteran's ailments are due to an obscure Gulf War exposure (a mysterious, poorly understood and involuntary risk) versus the chance they are due to smoking a pack of cigarettes per day for twenty years (a well-known, well-understood and voluntary risk) is likely to elicit patient outrage. This will diminish the chance that they will return to see you, much less adhere to your medical recommendations.

Outside Noise

Outside noise is produced by the peripheral or contextual issues that distort the risk message. For example, discussing chronic illness with a Gulf War veteran or a woman with silicone breast implants is a different matter from discussing it with the average patient. Of course, this is because the Gulf War and silicone implants have been the focus of intense scientific, governmental and media scrutiny as potential sources of illness (see Table 4). Clinicians who discount or overlook the context of the risk discussion do so at their own and, unfortunately, the patient's peril.



**TABLE 4
MEDIA TRIGGERS.**

A possible risk to public health is more likely to become a major media story if the following factors are (or can be made) prominent:

- questions of blame;
- alleged secrets and attempted cover-ups;
- human interest through identifiable heroes, villains, dupes, victims, etc.;
- links with existing, high-profile issues or personalities;
- conflict;
- signal value – the story as a portent of further ills (“What next?”);
- many people exposed to the risk, even if at low levels (“It could be you.”);
- strong visual impact (pictures of suffering); and
- links to sex and/or crime.

* Bennett, P: Understanding responses to risk: some basic findings. *Risk Communication and Public Health*. P. Bennett and K. Calman, Editors. Oxford University Press, New York; 1999.

Summary

The signal theory provides a simple model to understand the ways patients perceived health risk. Clinicians may find a useful approach to convey information to Gulf War (and other) veterans in settings that do not entail mutual mistrust, differential interpersonal power or perceived crisis.

References

National Research Council, Committee on Risk Perception and Communication. *Improving Risk Communication*. National Academy Press, Washington, DC; 1989.

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CHAPTER 3 STUDIES OF GULF WAR VETERANS' MORTALITY, MORBIDITY AND REPRODUCTIVE HEALTH

Introduction

Researchers investigating Gulf War veterans' health face many challenges, including the general absence of any specific, objective, clinically-relevant findings, the absence of a case definition that is unique to Gulf War veterans' illnesses, and the absence of documented exposure data for this population. Compounding these problems, well-documented and accessible baseline health data has not been routinely available for military populations. Consequently, researchers have had to rely upon self-reported symptom and exposure data as the basis of most of the research on the health impact of the Gulf War.

Nevertheless, findings from most published studies that have examined Gulf War veterans' health have been remarkably consistent, regardless of the methodology employed, which significantly enhances their overall validity. Consistent findings include:

- cause-specific mortality for Gulf War veterans following the war has been unremarkable, compared to non-deployed veterans or veterans from other deployments;
- active duty and reserve personnel deployed to the Gulf War report nearly all assessed symptoms at higher rates than comparison groups;
- Gulf War veterans are more likely to rate their overall health status as poorer since the Gulf War, compared to their non-deployed peers;
- frequently-reported symptoms include fatigue, cognitive difficulties, headaches, myalgias and arthralgia, mood disturbances, and sleep problems;
- that in general, Gulf War veterans are two to three times more likely to report these symptoms than comparison groups; and
- most published studies do not indicate that Gulf War veterans are at greater risk for reproductive health problems, compared to controls, although relevant data still is being collected.



3A. Mortality Among U.S. and U.K. Gulf War Veterans

Both U.S. and U.K. Gulf War veterans have consistently reported a wide variety of sometimes debilitating health problems. Nevertheless, these reports have not yet been reflected as significantly higher mortality from disease-related causes, including cancers and infectious diseases.(Table 1)

A cause-specific postwar mortality study of all 695,516 U.S. Gulf War veterans' compared to 746,291 non-Gulf veterans showed the former had significantly greater all-cause mortality (controlling for potential confounders, including age, gender, race and military variables¹.) This excess mortality was attributable mainly to external causes, including all types of accidents and specifically motor vehicle accidents. Both male and female U.S. Gulf War veterans were at greater risk of deaths from accidents following the Gulf War, and especially motor vehicle accidents (MVA). There was no observed excess of suicides, homicides or deaths from disease-related causes, and risk of death from infectious and parasitic diseases was significantly lower among the Gulf War veterans. Interestingly, cause-specific mortality rates were the same for Gulf War veterans deployed either before or after the March 1991 Gulf War cease-fire date. VA's mortality studies of Gulf War veterans remain ongoing to evaluate the risks of diseases with a long latency period, such as cancer.

TABLE 1
PUBLISHED U.S. AND U.K. GULF WAR VETERAN MORTALITY STUDIES

Authors (Year)	Study Design (Nationality)	Description	Results
Helmkamp 1994 (116)	Cohort (U.S.A.)	A study of fatal battle and non-battle casualties from 1-17-91 through 2-28-91 among approximately 540,000 active duty U.S. military personnel deployed to the Persian Gulf.	154 killed in battle, including 35 from friendly fire; 65 died from non-battle causes, including 55 from accidents and six from illness.
Writer, et al. 1996 (115)	Cohort (U.S.A.)	A study of cause-specific mortality rates among 688,702 active duty personnel deployed to the Persian Gulf from 8-1-90 through 7-31-91, and all other troops serving elsewhere during the same period.	The risks of death from injuries (SMR, 118; 95% CI 101-134) and unintentional injuries (SMR, 154; 95% CI, 132-177) were significantly higher among Gulf War veterans.
Kang and Bullman, 1996 (1)	Cohort (U.S.A.)	A study of postwar mortality through 9-30-93 among 695,516 Gulf War veterans and 746,291 other veterans.	Gulf War veterans had significant excesses of death from all external causes (RR, 1.17; 95% CI 0.8-1.27) and from motor vehicle accidents (RR, 1.31; 95% CI, 1.14-1.49), while mortality from disease-related causes was lower (RR, 0.88; 95%CI, 0.77-1.02).
Macfarlane et al. 2000 (13)	Cohort (U.K.)	A study of postwar mortality from 4-1-91 through 3-31-99 among 53,462 Gulf War veterans and an equal number of non-Gulf War veterans.	Mortality from external causes was higher ((MRR, 1.18; 95% CI, 0.98-1.42), while mortality from disease-related causes was lower in the Gulf War cohort (0.87, 0.67-1.11).



A population-based survey of 30,000 Gulf War era veterans indicated that since the war, Gulf War veterans were more likely to have a serious accident, injury or illness compared to non-Gulf War veterans.^{2,3} Furthermore, a smaller portion of Gulf War veterans who died from motor vehicle accidents used seat belts at the time of the fatal accident than non-Gulf War veterans who died from MVAs.⁴ VA researchers analyzed data from 549 Gulf War veterans and 398 non-Gulf War veterans who died from motor vehicle accidents (MVA).⁴ Gulf War and non-Gulf War veterans were compared on numerous factors, including age, race, gender, marital status, driver status (driver vs. passenger), vehicle type, speed, alcohol and drug measures, seat belt use and nature of collision (fixed object vs. moving vehicle).

Gulf War veterans who died from MVAs were found to be less likely to have used seat belts, motorcycle helmets or made crash-avoidance maneuvers. They were more likely to have been speeding, have measurable alcohol blood levels, been involved in single vehicle crashes, have collisions with fixed objects, be involved in rollovers and ejections and to have previous convictions for driving under the influence. Gulf War veterans also were more likely to have died at the scene of the accident or within one hour of medical attention.

Both U.S. Gulf War and non-Gulf War veterans experience significantly lower mortality compared to the U.S. general population. This finding is consistent with the “healthy-soldier effect” that has been reported in studies of other veterans.⁵⁻⁸ A recent study of veterans who were on active duty in 1986 reported that their mortality was half that of a civilian comparison group.^{6,9}

The initial excess mortality seen in the years following the Gulf War from motor vehicle accidents has diminished, and by the 6th year of follow-up (May 1996 - December 1997), the relative mortality from MVAs had fallen below 1.0.¹⁰ Further, researchers reported no statistically significant difference in cause-specific mortality among Gulf War veterans for any other causes of death. An initial increase in post-war mortality due to accidents also was observed in an earlier mortality study of Vietnam veterans in which the excess mortality due to MVAs was most pronounced in the first five years after Vietnam service, then decreasing the sixth year of follow-up to the levels found in the non-Vietnam group.¹¹

There is no clear explanation for this consistently observed initial increase in mortality rates from accidents following return from military deployments. Nor is it clear why this initial increase in mortality from accidents invariably disappears within less than a decade.

Mortality rates during the Gulf War were remarkably low for any modern U.S. military mission. Battle and non-battle fatalities totaled 219 service members (212 men and seven women) killed during the six-week combat phase of Operations Desert Shield and Desert Storm (January 17, 1991 through February 28, 1991).¹² Of these, 154 (148 men and six



women) were battlefield casualties and 65 were non-battlefield casualties. Fifty-five of the 65 non-battle deaths resulted from accidental injuries. Other causes included six illnesses, two suicides and one homicide.

Mortality also has been examined among non-U.S. Gulf War veterans. Over 30 countries provided air, sea or ground forces to the Gulf War. The United Kingdom (U.K.) contributed approximately 53,000 troops, the second largest number from Western countries (after the U.S.). Both U.S. and U.K. Gulf War veterans show remarkably similar excess mortality from accidents, especially motor vehicle accidents (including accidental poisonings, but not homicide or suicide). Thus, post-war mortality among British Gulf War veterans compared all 53,462 British Gulf War veterans to era controls reported higher mortality from external causes in veterans.¹³ These deaths primarily were due to a higher number of deaths from motor vehicle accidents, air/space accidents, deaths associated with submersion or suffocation. As with U.S. veterans, mortality from disease-related causes was lower compared to controls, and there was no excess of deaths among Gulf War veterans from suicide or from injury from unknown cause.

Mortality among U.S. Gulf War veterans is relatively straightforward to study because both Gulf War veterans and non-Gulf War veterans have been well-documented by the U.S. Department of Defense (DoD), and excellent sources are available for vital status data.¹⁴ Death certificates are reliable sources for vital status ascertainment, although their accuracy in recording cause of death may be variable.^{15, 16, 11} In VA's first mortality study, vital status was obtained for about 89 percent of possible subjects, including both Gulf War and non-Gulf War veterans.¹ Moreover, data on cause of death was obtained for equally high percentages of both groups of veterans (93.7 percent of Gulf War veterans and 93.4 percent of non-Gulf War veterans). Finally, VA's mortality study had sufficient statistical power to detect small-to-moderate increased risks of cause-specific mortality.¹



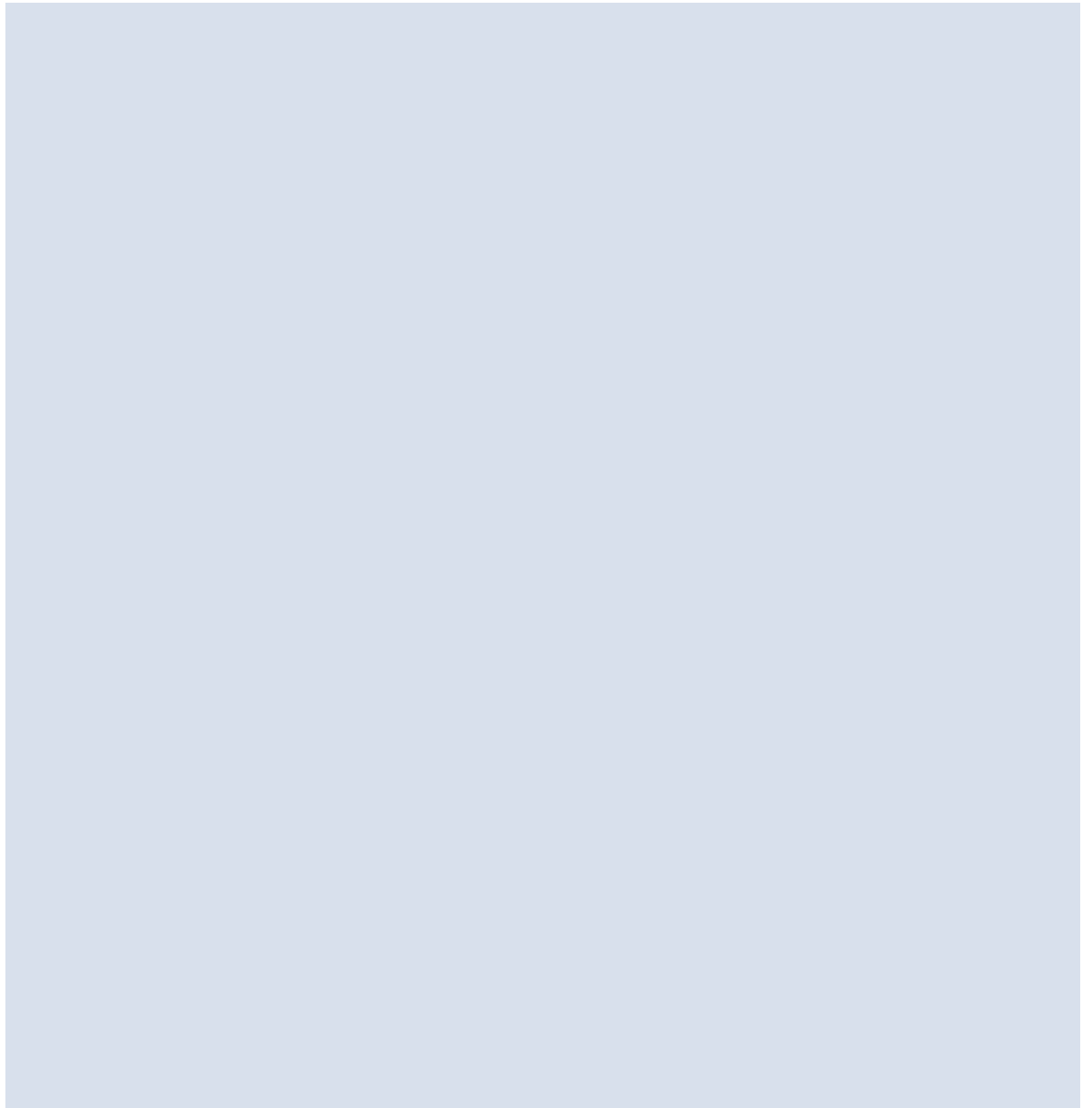
3B. Morbidity Among Gulf War Veterans

Early media reports of Gulf War veterans' health problems included a January 1992 "outbreak" of unexplained symptoms among members of the 123rd Army Reserve Unit in Indiana (subsequent investigation of that reserve unit found no evidence for the outbreak of a unique disease.)¹⁷ Although well-defined diseases have been identified among some Gulf War veterans (e.g., 12 cases of viscerotropic leishmaniasis),¹⁸ some Gulf War veterans' health complaints involve non-specific symptoms that are not readily medically explained.

TABLE 2
SPECIAL GULF WAR VETERAN HEALTH REGISTRY EVALUATIONS

Sponsor	Registry Name	Start Date	Number of Veterans Evaluated as of June 2000	Number Deployed
United States Department of Veterans Affairs	Persian Gulf Veterans Health Registry (52)	August 1992	70,000+	697,000
United States Department of Defense	Comprehensive Clinical Evaluation Program (7)	June 1994	53,000+	
United Kingdom Ministry of Defense	Gulf War Medical Assessment Programme (9)	July 1993	3,000+	53,000
Canada Department of National Defense	Canadian Gulf War Registry (53)	January 1995	226+	4,500

Following the Gulf War, both VA and DoD established Gulf War health care registries (described in Chapter 2 and Table 2). Registry data have proven most useful for documenting both the wide range of self-reported symptoms, exposures and the most commonly recorded diagnoses. They have helped researchers develop hypotheses for follow-up epidemiological studies.¹⁹⁻²² However, they are much less useful for characterizing the overall health of the average Gulf War veteran, due to volunteer bias, extensive and sometimes sensational media reports, recall bias for self-reported symptoms and exposures, the absence of a control group and other potential confounders that inevitably are associated with health registry data.^{20, 23, 25,}





The most frequently reported symptoms and diagnoses from VA, DoD and U.K. registries are remarkably similar. Fatigue, rashes, headache, muscle and joint pain, and cognitive problems are all common (Table 3), as well as related, often nonspecific, diagnoses (Table 4). These broadly consistent findings illustrate the wide variety of apparently unrelated symptoms and illnesses experienced by some Gulf War veterans.²⁵

TABLE 3
PREVALENCE OF FREQUENTLY REPORTED SYMPTOMS IN VARIOUS
GULF WAR VETERAN REGISTRIES

Symptom	U.S. Department of Veterans Affairs (10) (n = 52,835)	U.S. Department of Defense (n = 53,032)*	United Kingdom (n = 1000)(9)	Canada (n = 104)†
	Symptom prevalence (%)			
Fatigue	20.8	37.2	42.1	86.5
Skin rash	18.4	24.0	19.4	47.1
Headache	18.0	32.7	25.6	65.4
Muscle and joint pain	16.8	40.9‡	39.5	75.0
Cognitive problems	14.0	33.5**	26.1	84.6
Shortness of breath	7.9	19.0	24.3	33.0
Sleep disturbance	5.9	29.1††	21.2	74.0
Diarrhea and other gastrointestinal	4.6	27.0 ‡‡	21.8	55.8
No complaint	12.3	41.1***	7.4	0

* As of May 31, 2000.

† From 104 veterans evaluated at Ottawa's Gulf War Clinic, April 1995 to December 1997.

‡ Answered "yes" to "muscle pain," "joint pain" or both.

** Answered "yes" to "difficulty concentrating," "memory loss" or both.

†† Answered "yes" to any of the following: "sleep disturbance," "loud snoring" or "stopped breathing while sleeping."

‡‡ Answered "yes" to "abdominal pain," "diarrhea" or both.

*** Did not answer "yes" to 18 questions about symptoms, including "Do you have any other symptoms?"



TABLE 4
PERCENT DISTRIBUTION OF SELECTED DIAGNOSES FOR GULF WAR
VETERANS PARTICIPATING IN A HEALTH REGISTRY

Diagnoses	ICD-9 code‡	U.S. Department of Veterans Affairs* (n = 69,941) % of diagnoses	U.S. Department of Defense† (n = 53,032)
None	**	27.0	29.5
Malaise and fatigue	780.7	22.0	8.4
Headache	784.0	21.0	6.2
Pain in joint	719.4	13.2	12.7
Sleep disturbances	780.5	7.9	7.9
Depressive disorder, not elsewhere classified	311	4.1	4.9
Lumbago	724.2	4.0	6.1
Psychalgia	307.8	3.9	7.7
Other specified adjustment reactions	309.8	3.9	3.6
Essential hypertension, unspecified	401.9	3.6	2.8
Contact dermatitis and other eczema, unspecified cause	692.9	3.6	2.6
Unspecified sinusitis, (chronic)	473.9	3.2	1.9
Other and unspecified non-infectious gastroenteritis and colitis	558.9	2.8	1.5
Asthma, unspecified	493.9	2.7	2.5
Migraine, unspecified	346.9	2.6	3.8
Allergic rhinitis, cause unspecified	477.9	2.5	3.4
Anxiety states	300.0	2.4	1.7
Osteoarthritis, unspecified	715.9	2.2	4.4
Alopecia	704.0	2.1	2.4
Irritable colon	564.1	1.9	3.7

* In the VA registry, a special non-ICD-9 code "DX111" was used, as well as ICD-9 code V65.5 (person with feared or anticipated psychological disorder) to indicate veterans with no diagnoses. All are considered as missing.

† Percentage of Gulf War veterans who completed the VA registry examination as of September 30, 1999.

‡ Four-digit code from the International Classification of Diseases, Ninth Revision, Clinical Modification, 3rd Edition (1990).

** Data as of May 30, 2000. Diagnoses were reported in the any of the primary or six secondary diagnostic fields. A code of "xxx.xx" was interpreted as missing.

Table 5 continued on next page



Research on Gulf War Veterans' Health Status

To adequately characterize the health of Gulf War veterans as a whole requires well-designed, population-based epidemiological studies^{27, 28, 3, 29, 30-38} (Table 5). In contrast to health registries, population-based epidemiological studies use comparison group controls, including non-deployed military personnel, service members deployed to other regions during the Gulf War and military participants from other conflicts to compare prevalence rates across various groups. Published population-based studies have included mail and telephone surveys, in-person questionnaires and interviews and physical examinations. Participants range from a few hundred to over 20,000, with response rates (31 percent) to very good (76 percent).³⁹ The most useful studies have the following characteristics: they are randomly sampled population-based, use a suitable control group of military personnel not deployed to the Gulf, and employ some standardized or validated survey instruments that allow comparisons to other populations or other studies.

**TABLE 5
PUBLISHED STUDIES ON SYMPTOMS REPORTED BY GULF WAR VETERANS**

Study	Population	Survey Type	# of Respondents	Response Rate	Five Most Frequent Symptoms Reported by Gulf War Veterans
Stretch, et al. 1995 (31)	Stratified random sample of members from the Ft. Devens Gulf War cohort (U.S. Army active, Reserve and National Guard) and the New Orleans Gulf War cohort (represents all services active, Reserve, and National Guard), and members of a Maine National Guard unit from an air ambulance company deployed to Germany	Anonymous questionnaire distributed at the unit level	4,334	31%	<ul style="list-style-type: none"> • Headaches • Sinus troubles • Head colds • Aching joints/ bones • Sore throat
Sostek, et al. 1996 (32)	All Canadian Gulf War veterans; Canadian forces who served elsewhere during time of Gulf War	Questionnaire ^a	101	74%	<ul style="list-style-type: none"> • Fatigue • Joint pains • Loose or frequent Stools, excessive gas • Abdominal pain
Fukuda, et al 1998 (27)	Members of 14 regular active-duty U.S. Navy Seabee commands at Port Hueneme, CA and Gulfport, MS who served from September 1990 until time of survey	In person anonymous questionnaire	3,723	60.5% ^b	<ul style="list-style-type: none"> • Sinus congestion • Headache • Fatigue • Joint pain • Difficulty remembering/ Concentrating
Iowa Persian Gulf Study Group, 1997 (33) Doebbeling, et al. (34)	British regular and Reservist of the Royal Navy, Army, and Royal Air Force who served between September 1, 1990 and June 30, 1991; military personnel who served in Bosnia between April 1, 1992 and February 6, 1997	Telephone survey	3,696	76%	<ul style="list-style-type: none"> • Feeling tired • Multiple joint pains/ Aches • Lack of energy • Need to rest more • Muscle pain

Table 5 continued on next page



continued

PUBLISHED STUDIES ON SYMPTOMS REPORTED BY GULF WAR VETERANS


Study	Population	Survey Type	# of Respondents	Response Rate	Five Most Frequent Symptoms Reported by Gulf War Veterans
Pierce 1997 (35)	Members of Danish peacekeeping UN task force who were stationed in Persian Gulf area between August 2, 1990 and December 31, 1997; Danish armed forces who served during the time of the Gulf War.	Mail survey administered two and four years after the war	Time 1 - 484	Time 1 - 76% ^b	
			Time 2 - 456	Time 1 - 71% ^b	
Proctor, et al. 1998 (36)	All U.S. troops deployed to the Persian Gulf area during the Gulf War; 50% random sample of all troops who were in the military between September 1990 and May 1991 and not deployed to the Persian Gulf.	In person questionnaires, neuropsychological testing, psychiatric interviews	343	53% ^b	<ul style="list-style-type: none"> • Difficulty concentrating • Joint pains • Headaches • Inability to fall asleep; • Backaches
Goss Gilroy 1998 (37)		Mail survey	6,552	64.5%	<ul style="list-style-type: none"> • Cognitive dysfunction^c • Depression • Fibromyalgia • Respiratory disease • Alcohol abuse
Gray, et al. 1999 (29)		In person questionnaire, clinical specimens, selected physical measurements	1,497	53%	<ul style="list-style-type: none"> • Unusual fatigue • Forgetfulness • Trouble sleeping • Sleepy all the time • Rash
Unwin, et al. 1999 (28)		Mail survey	8,195	65%	<ul style="list-style-type: none"> • Unrefreshing sleep • Irritability/outbursts of anger • Headaches • Fatigue • Sleeping difficulties

TABLE 5



continued

PUBLISHED STUDIES ON SYMPTOMS REPORTED BY GULF WAR VETERANS

Study	Population	Survey Type	# of Respondents	Response Rate	Five Most Frequent Symptoms Reported by Gulf War Veterans
Ishey, et al. 1999 (38)		Mail survey, interview, health examination	917	75% ^b	<ul style="list-style-type: none">• Concentration/memory difficulties• Abnormal feeling of fatigue• Unrefreshing sleep• Unusual feeling of fatigue during the day• Depression/sadness
					
Kang, et al. 2000 (3)		Mail survey, telephone interview with non-respondents, medical record review	20,917	70%	<ul style="list-style-type: none">• Runny nose• Headache• Unrefreshing sleep• Anxiety• Joint pain

^a Method for distributing questionnaire not specified.

^b Single response rate calculated based upon information provided in the publication on total number of eligible subjects and number of participants.

^c Reflects symptom patterns suggestive of prior identified medical and psychiatric conditions.



VA initiated the National Health Survey of Gulf War era Veterans and Their Families in large part as a means of overcoming the limitations inherent in a registry. The goal of this cross-sectional health-outcomes survey is to reliably evaluate the health of all Gulf War veterans. It is a true, population-based sample of 15,000 U.S. Gulf War veterans and 15,000 Gulf War era veterans. In comparison with their peers, Gulf War veterans report higher prevalence of functional impairment, health care utilization, symptoms and medical conditions and a higher rate of low, general health perception.³ Gulf War veterans also report greater rates of adverse reproductive health outcomes — self-reported data that is currently being validated.^{3.b}

DoD hospitalization studies are another example of epidemiological study design used to evaluate postwar morbidity among Gulf War veterans. Such studies have not identified unusual Gulf War-related diagnoses, but they have shown that the most important predictors of postwar hospitalization are female gender, prewar hospitalization, healthcare occupation, enlisted rank, service in the Army, and low-rank status.⁴⁰⁻⁴²



A 1996 DoD study examined postwar hospitalizations during the 25-month period following the war for Gulf War veterans compared to non-deployed veterans.⁴⁰ Gulf War veterans remaining on active duty had increased but inconsistent risk for postwar hospitalizations, possibly the result of deferred medical care or other well-understood postwar conditions. In a 1996-97 postal survey of Gulf War veterans' hospitalizations, comparison of 11,441 Gulf War veterans to 9,476 non-deployed veterans found a higher proportion of Gulf War veterans reporting a hospitalization due to illness during the previous year [ratio = 1.22; 95 percent confidence interval (CI) 1.10 to 1.34].³ Similarly, a 1997-99 postal survey of hospitalizations of 12,049 Seabees, including 3,831 Gulf War veterans who served during the Gulf War period found that 38 percent of Gulf War veterans reported one or more hospitalizations, compared to 35 percent of non-deployed veterans.⁴³

Hospitalization data showed no evidence of increased risk among hospitalized Gulf War veterans for many diagnoses, including cancers such as testicular cancer.⁴⁴ Evaluation of hospitalizations among Gulf War veterans for new or unidentified conditions found an increased hospitalization risk during the 50-month postwar period beginning late in 1994.⁴¹ However, researchers concluded that the increase was an artifact of DoD's Gulf War veteran registry program that admitted veterans as inpatients for completing their diagnostic evaluation, rather than for any illness.

Similarly, review of 30,539 DoD mental health hospitalizations from June 1991 through September 1993 for unusual mental health morbidity found that Gulf War veterans were more likely to be admitted for alcohol-related disorders, drug-related disorders and acute reactions to stress, compared to their non-deployed peers.⁴⁵ The strongest predictor of postwar mental health hospitalization was prewar mental health hospitalization. With the exception of alcohol-related disorders, researchers found no association between service in combat units during the Gulf War and risk of postwar mental health hospitalization.

Other investigators also report moderate, transient increases of postwar ambulatory mental health or social problems among Gulf War veterans.⁴⁶ Review of October 1988 through July 1997 DoD hospitalization data relative to the onset of systemic lupus erythematosus, amyotrophic lateral sclerosis and fibromyalgia in Gulf War veterans compared to non-deployed peers found no evidence that Gulf War veterans were more likely to be hospitalized for any of these three conditions.⁴⁷

Most DoD hospitalization studies only examined those individuals who were eligible for DoD hospital care and therefore are not truly population-based. However, a 1998 study reviewed hospitalization data for Gulf War veterans and non-deployed veterans at DoD, VA and selected nonfederal California medical facilities.⁴⁸ Researchers found no evidence that either Gulf War veterans who remained on active duty or who had separated from military



service following the war were suffering increased hospitalizations for infectious diseases, cancers, endocrine diseases, nervous system diseases, blood diseases, circulatory system diseases, musculoskeletal diseases or skin conditions.

However, Gulf War veterans had proportionally more hospitalizations for fractures and bone and soft tissue conditions in DoD and California hospitals, and for respiratory diseases, digestive diseases and vague symptom diagnoses in VA hospitals. Researchers concluded that these findings are biologically plausible, but may be the result of as yet unidentified confounding risk factors.

In another study, long-term health effects from possible exposure to chemical warfare nerve agents in March 1991 at Khamisiyah, Iraq, were evaluated using DoD hospitalizations data through September 1995.⁴² This involved 348,291 U.S. Army Gulf War veterans. Despite absence of reports of acute nerve agent toxicity, possible latent morbidity from sub-clinical nerve agent exposure was a concern. Potentially-exposed Gulf War veterans were not found to be at increased risk of hospitalization for any cause, for diagnoses in any one of 15 ICD-9 large categories or for diagnoses thought most likely to be associated with latent manifestations of sub-clinical nerve agent exposure.

Outpatient visits of Gulf War veterans also have been examined. In a postwar healthcare utilization postal survey of 4,334 Gulf War veterans and their non-deployed peers, both active duty and reserve Gulf War veterans reported higher rates of physician visits in the two weeks before the survey.³¹ A survey of more than 20,000 U.S. Gulf War veteran and era service personnel found a higher proportion of Gulf War veterans reporting a clinic visit due to illness.³ Similarly, a survey of 3,113 Canadian Gulf War veterans and 3,439 non-deployed veterans, asking about contacts with healthcare professionals, hospital emergency room visits and hospital admissions during the previous 12 months, found no evidence for increased healthcare utilization among Gulf War veterans.³⁷ However, more Gulf War veterans reported using prescription drugs during the two weeks before the survey, compared with non-deployed peers (26.7 percent vs. 23.6 percent).

Limitations of Self-Reported Exposure and Self-Reported Health Outcome Data

Potential sources of bias or systematic error affecting the validity and generalizability of epidemiological studies of Gulf War veterans include differential recall, response and participation biases. Essentially all large population-based studies on Gulf War veterans report significant associations between nearly all self-reported exposures and all evaluated health outcomes.^{33, 29, 28} However, validating these observations is hampered by the virtual absence of objective exposure and health data, leading to a reliance upon self-reported exposure information (often years after the fact) and self-reported health outcomes.



Recall bias is an obvious though difficult-to-evaluate concern. In one study, self-reports of possible exposure to “poison gas” were associated with reporting of more symptoms.⁴⁹ Similarly, belief that biological or chemical weapons were used during the Gulf War, self-reported use of the anti-nerve agent drug pyridostigmine bromide (PB), or self-reported insect repellent use were associated with illnesses among Air Force veterans.⁵⁰ Reports on a U.S. Naval reserve construction battalion (Seabees) found associations between self-reported exposures to several chemicals including chemical warfare agents and several symptom groups or factors.⁵¹ On the other hand, multiple independent review committees have been unable to attribute Gulf War veterans’ symptoms to exposure to any particular stimulus or agent.^{39, 52}

Low response rates (e.g., less than 70 percent) also affect the possibility of generalizing results to all veterans.³⁹ Many studies have failed to obtain good participation rates — response rates have ranged from 31 to 76 percent. Reasons for poor participation rates include difficulty in locating or interviewing subjects (some may be too ill to participate) or veterans may not be motivated to participate for other reasons. Gulf War veterans still on active duty may under-report illness to keep their active duty status or they may selectively separate from active duty as a result of their illness. Ill Gulf War veterans may be more likely to participate in studies and more likely to recall health concerns and possible exposures, compared to well veterans.

Significantly, unexplained illnesses have not been correlated with any specific period during Operations Desert Storm and Desert Shield. Although Gulf War exposures such as personal insecticides, PB and others should vary over time, no differences in the rates of unexplained illness by deployment period were found in one study.⁵³ Deployment itself may have some effect; U.K Gulf War service members who reported receiving multiple vaccines after deployment were at increased risk for reporting multiple symptoms, including multi-symptom illness, lower health status and decreased physical functioning.

However, receiving multiple vaccines *prior* to deployment was associated *only* with post-traumatic stress disorder.^{28, 54} A study conducted by the state of Kansas to determine if Kansas Gulf War veterans experienced a greater burden of health problems compared to era veterans found that Gulf War veterans were significantly more likely to report their health status had declined since the war and to report greater rates of each of 37 symptoms surveyed as being persistent problems in the previous year, compared to era veterans.^{54a} Perhaps not surprisingly, veterans who served on board ship were less likely to report symptoms, compared to those who served in Iraq or Kuwait, regardless of when they left the Gulf region. Finally, they reported an association with symptom reporting and self-reported exposure to vaccines during the war, although the significance of this was unclear. Similarly, although



Danish troops were primarily involved in peace-keeping operations only after the war, a variety of health complaints have been reported among those troops, as well.³⁸

Congress and the media have sharply focused national attention on the health impact of the Gulf War.⁵⁵⁻⁵⁸ Media attention may cause those involved to become more attentive to symptoms and to more thoroughly search their memories for environmental events or other potential explanations or causes. Researchers report increased enrollment in both DoD and VA health registries during periods of high media attention to Gulf War issues.²⁰ The rate of reporting the use of insect repellents during the Gulf War was correlated to specific media events, although overall, there was little or no relationship between Gulf War media events between 1995 and 1997 and self-reported exposures.²³



3C. Medically Unexplained Symptom-Based Illnesses Among Gulf War Veterans

Researchers have made significant progress in documenting the prevalence of symptom-based health problems among Gulf War veterans in comparison to appropriate control groups. Research is hampered by the difficulty of developing case definitions for symptom-based conditions which lack objective criteria and by the lack of good exposure data.⁵⁹ Nevertheless, this effort has identified a group of medically unexplained physical symptoms among Gulf War veterans, characterized primarily by fatigue, cognition problems and musculoskeletal complaints. In essentially every epidemiological study, Gulf War veterans report greater rates of virtually every symptom they are asked about.

Prevalence rates for headache, fatigue, cognitive disturbance, pain and sleep problems in Gulf War veterans have been reported to be from as high as 30 to 50 percent^{27, 28, 3} to as low as 15 to 20 percent.²⁹ This range may be due to differences in study design, sampling, instruments and participation rates, although many other factors also can influence symptom reporting. In fact, most popularized concepts of Gulf War illnesses focus on multi-symptom, chronic and difficult to diagnose conditions, even though such conditions are less common in this population, compared to more conventional and diagnosable illnesses.

Symptom-based illnesses share many characteristics with other well-described symptom-based conditions that are common in the general U.S. population, especially chronic fatigue syndrome (CFS), fibromyalgia (FM) and multiple chemical sensitivity (MCS). In general, such symptom-based conditions are rarely associated with objective physical signs, laboratory abnormalities or other objective, generally accepted diagnostic criteria. Considerable overlap exists between the symptoms of CFS, FM and MCS, which may represent different points on a continuum of illness or different manifestations of the same underlying condition.^{60, 61}

Several studies have specifically assessed CFS, FM and MCS among subgroups of Gulf War veterans. The results are not generalizable to all Gulf War veterans because these studies have relied primarily upon non-representative, self-selected subjects from Gulf War registry populations. In a cross-sectional survey of 41 outpatients from a single VA medical center, Gulf War veterans who reported poor health were more likely to also report chemical sensitivity, compared to healthy Gulf War veterans.⁶² Similarly, of 72 participants in the VA Gulf War registry reporting severe fatigue and chemical sensitivity, 33 were diagnosed as CFS, of whom 14 also met criteria for MCS and two received a concurrent diagnosis of fibromyalgia.⁶³ MCS rates in veterans with CFS were not significantly different than that among non-veterans with CFS.



In a larger sample of VA registry participants ($n = 1,161$), 16 percent reported symptoms consistent with CFS and 13 percent reported symptoms characteristic of MCS.^{64a} In a Centers for Disease Control and Prevention (CDC) study of four Air Force units, 8 of 158 (5 percent) clinically evaluated Gulf War veterans met criteria for CFS.²⁷ Of Air Force personnel who completed the in-person survey, 43 percent of Gulf War veterans and 17 percent of non-deployed personnel reported current fatigue that had lasted 6 months or longer. Five percent of the Gulf War veterans reported symptoms of chemical sensitivity, compared to two percent of non-deployed personnel.

In a large-scale epidemiological study of Iowa Gulf War veterans, chronic fatigue was reported at a lower prevalence compared to the CDC Air Force study (one to three percent of Gulf War veterans and 0.2 - one percent of non-deployed personnel.)³³ However, five percent of Gulf War veterans and three percent of non-deployed troops reported chemical sensitivity symptoms paralleling the Air Force study findings.^{64b} Eighteen to 24 percent of Gulf War veterans in the Iowa study reported FM symptoms, compared to nine to 13 percent of non-deployed personnel controls.³³ The 169 (4.6 percent) Iowa study subjects meeting MCS criteria also reported greater rates of medical disability, unemployment, physician and emergency department visits, inpatient hospital stays and impaired function across a broad range of health domains, compared to subjects who did not meet MCS criteria.⁶⁵

Three percent of U.K. Gulf War veterans reported symptoms consistent with CFS, compared with 0.8 percent of Bosnia and 0.8 percent of era veterans.²⁸ Relatively few U.K. subjects reported symptoms of chemical sensitivity (0.8 percent of Gulf War veterans, 0.4 percent of Bosnia veterans, and 0.3 percent of era veterans), and these symptoms were not associated with deployment status. Canadian Gulf War veterans also were more likely than controls to report symptoms of CFS, FM and MCS.³⁷

Symptom-based health problems are commonly observed in all adult populations.^{66, 67} Such symptom-based conditions are similar to those commonly seen in primary care practice, which also include complaints of chronic fatigue, headache, myalgias and arthralgia and cognitive disturbances. Similar illnesses have been noted among veterans of other military deployments dating back to the U.S. Civil War.⁶⁸ In fact, medically unexplained physical symptoms (symptoms present without objective physical examination or laboratory test abnormalities) are remarkably prevalent among all Americans.⁶⁹ CFS, FM and MCS occur at significant rates in the general adult U.S. population (CFS from 0.2- 0.6 percent;^{70, 71} fibromyalgia one to four percent).^{72, 73} A population-based survey of four U.S. communities found that 32 percent of respondents reported headaches, 23 percent reported dizziness, 25 percent reported headaches and 25 percent reported fatigue; 31 percent of symptoms were medically unexplained.⁶⁷



According to the National Ambulatory Medical Care Survey, physical symptoms accounted for over half of all U.S. ambulatory care visits.⁷⁴ Multiple studies demonstrate that medically unexplained physical symptoms are strongly associated with functional impairment or disability, health care utilization, psychosocial distress and psychiatric disorders.⁷⁵⁻⁸⁰ With all symptom-based illnesses, research is hampered by problems establishing a workable case definition that can effectively categorize subjects with a unique illness.⁶⁹ Given the results of VA and DoD registries, case definitions for Gulf War illnesses must reflect the variety of somatic symptoms reported by some Gulf War veterans following the end of the war that are not generally accompanied by physical signs or laboratory abnormalities. Case definitions for symptom-based illnesses, such as CFS and FM, rely on consensus definitions established by expert panels based upon their clinical and research experience.⁸¹⁻⁸³ Research with Gulf War veterans has relied more on statistical, data-driven approaches, such as factor analysis, for developing working case definitions.

Use of Factor Analysis in Evaluating Unexplained Illnesses

Factor analysis has been used by many different researchers as a tool for investigating Gulf War veterans' illnesses. It is a statistical technique developed for data reduction, scale development and for identification of relationships among multiple variables.⁸⁴ In 1997, one research group using this approach reported three primary illnesses based upon novel combined factors in 249 Gulf War veterans from the 24th Reserve Naval Mobile Construction Battalion selected because of significant health complaints shortly after the Gulf War.^{51, 85} Researchers surveyed 41% of the Seabee unit's 606 Gulf War veterans. Illnesses were labeled as "impaired cognition" (characterized by problems with attention, memory, and reasoning, insomnia, depression, daytime sleepiness and headaches); "confusion-ataxia" (problems with thinking, disorientation, balance, vertigo and impotence); and "arthro-myoneuropathy" (joint and muscle pains, muscle fatigue, difficulty lifting and extremity paresthesia).

In a case-control study, 23 veterans identified with these "syndromes" scored lower on certain summary measures of neurologic function, compared to a group of 20 healthy Gulf War veterans and non-deployed controls.⁸⁶ Subsequent research has continued to focus upon these 43 veterans. Twenty-three sufferers from these syndromes were reported to perform worse than 20 healthy controls on a series of neurological tests, leading researchers to conclude that they had "generalized injury to the nervous system." Finally, the risk of Syndrome 1 was greatest among veterans who said they had worn flea collars during the war; Syndrome 2 (the worst of the three) was associated with self-reported exposure to nerve gas or PB; and the chance of suffering from Syndrome 3 seemed to increase with the use of a government-issued insect repellent that contained DEET."



Other researchers have tried factor analysis for evaluating symptom data from active duty Naval Seabees. Those studies identified five factors labeled as insecurity or minor depression, somatization, depression, obsessive-compulsive and malaise.¹¹⁷ The depression and malaise factors represented investigator-derived questions relating to symptoms of depression and symptoms commonly reported by Gulf War veterans (tender or swollen glands/lymph nodes, constipation, fever, sudden hair loss, chills, night sweats, sore throat and a validity symptom, earlobe pain), respectively.

More recently, researchers using factor analysis have defined a chronic, multi-symptom illness among 3,675 deployed and non-deployed Air Force personnel.²⁷ The chronic multi-symptom illness they defined includes one or more chronic symptoms (present for more than 6 months) from at least two of three symptom categories: fatigue, mood and cognition problems (feeling depressed, difficulty remembering or concentrating, feeling moody, feeling anxious, trouble finding words or difficulty sleeping), and/or musculoskeletal problems (joint pain, stiffness or muscle pain). Chronic fatigue was retained as a separate symptom category because of its consistent and central role in illness among Gulf War veterans.

Forty-seven percent of Gulf War veterans met this case criteria, compared to 15 percent of non-deployed subjects. This diagnosis was not unique to Gulf War veterans and was not associated with the factors such as the number of deployments to the Gulf War, the month or season of deployment, the duration of deployment, military occupational specialty, direct participation in combat or self-reported locality in theater. Finally, clinical examination found no significant physical or laboratory test abnormalities that could be associated with chronic, multi-symptom illness.

Factor analysis used in the study of Iowa Gulf War veterans also identified symptom factors in both subjects and controls.³⁴ Subjects selected from 889 different units widely distributed throughout the Gulf theater during the conflict reflected a broad range of potential exposures. Factor analysis identified three symptom factors, including “somatic distress” (characterized by joint stiffness, myalgias, polyarthralgia, numbness or tingling, headaches and nausea); “psychological distress” (feeling nervous, worrying, feeling distant or cut off, depression and anhedonia), and “panic” (anxiety attacks; heart racing, pounding or skipping; attacks of chest pain or pressure and attacks of sweating). Half (50 percent) of deployed and 14 percent of non-deployed service members reported health problems attributed to military service during 1990-91. These figures are similar to the proportion of Air Force veterans meeting the CDC working case definition of chronic, multi-symptom illnesses.



U.K. investigators have also described three similar symptom-cluster based factors characterized as mood-cognition symptoms (headaches, irritability, sleep difficulties, feeling jumpy, un-refreshing sleep, fatigue, feeling distant or cut off from others, forgetfulness, loss of concentration, avoiding doing things or situations and distressing dreams); respiratory system symptoms (inability to breathe deeply, fast breathing, shortness of breath at rest and wheezing); and peripheral nervous system symptoms (tingling in fingers or arms, tingling in legs or arms and numbness or tingling in fingers or toes)⁸⁷. Using this definition, U.K Gulf War veterans reported symptoms at greater rates, compared to non-deployed Gulf War era military personnel controls. But these symptoms also were not unique to deployed veterans, and appeared in veterans of the more recent Bosnia conflict.

In summary, in studies of active duty Navy Seabees, the Iowa, U.K. and Air Force studies, both Gulf War veterans and non-deployed era veterans report similar groups or patterns of self-reported symptoms, although at different rates. Importantly, identification of the same patterns of symptoms among deployed and non-deployed military personnel in each of these four population-based studies suggest that the health complaints of Gulf War veterans are similar to those of the general military and civilian populations. Factor analysis as a means of investigating Gulf War veterans' health has not shown any particular advantage over more conventional clinical assessments. Finally, clinical studies that assess characteristic physical and laboratory abnormalities based on biologically plausible etiologies, rather than relying on subjective criteria, are needed.

Cross-sectional, phone interviews and medical records review, two National Guard units (n=54 GWV births)

Discharge diagnostic data from military hospitals, 1991-93 (n=33,998 GWV births; 41,463 NDV births)

Discharge diagnostic data from military hospitals, postwar conceptions (n=34,069 GWV births; 41,345 NDV births). Cases ascertained through medical records review.

Self-reported postal survey to all GWV Canadian veterans (n=3,974 GWV conceptions; 4,326 NDV conceptions)



3D. Reproductive Health Among Gulf War Veterans

Anecdotal reports of adverse reproductive outcomes among Gulf War veterans raised concern about possible prenatal effects of hazardous exposures.^{55, 88-90} As in previous conflicts, some veterans believe that Gulf exposures affected their health and that of their children.⁹¹ Birth defects, fetal loss and infertility are the three most commonly studied adverse outcomes among Gulf War veterans. Most published studies on reproductive outcomes of Gulf War veterans do not support a hypothesis of major damage to male reproduction or of deleterious effects on the health of their offspring (Table 6). However, the majority of relevant evidence is still being gathered in the United States and the United Kingdom. VA's National Health Survey of Gulf War Era Veterans and Their Families reported that in comparison with their peers, Gulf War veterans report higher prevalence of functional impairment, health care utilization, symptoms and medical conditions, and a higher rate of low general health perception. Gulf War veterans also reported greater rates of adverse reproductive health outcomes — self-reported data that is currently being validated.^{3,b}

Many specific Gulf War environmental exposures also have been evaluated in other occupational settings and have been associated with possible reproductive health problems in pregnant women, e.g., via in-utero fetal exposure. Most (93%) Gulf War veterans are men, which focuses attention upon paternal wartime exposures. Occupational epidemiological and animal studies show that male exposure to various agents including heavy metals, solvents, or paints and pesticides may be associated with poor sperm quality, spontaneous abortion, birth defects and cancer in offspring.⁹²⁻⁹⁹ Possible mechanisms for these effects include gene mutation, chromosomal aberrations, seminal transfer of toxic agents or epigenetic events.

Birth Defects Among Children of Gulf War Veterans

Media accounts of an apparent cluster of birth defects among children of veterans from two Mississippi National Guard units led to the earliest studies of Gulf War reproductive health.¹⁰⁰ The prevalence of birth defects in those children were not significantly different from other state birth defects surveillance programs (three to five percent), although the number of cases in the Mississippi study was very small.

A larger study compared the prevalence of birth defects among 33,998 Gulf War veteran's infants to 41,463 infants of non-deployed veterans in U.S. military hospitals between 1991 and 1993.¹⁰¹ No differences were observed in the overall prevalence of major birth defects diagnosed at birth between Gulf War infants and control infants when stratified by organ specific defects, gender of military parent, race/ethnicity, marital status and branch of service. However, infants born in nonmilitary hospitals were not represented, and birth



defects were limited to those diagnosed during the newborn period, which account for just 40–60 percent of all birth defects. A study among wives of Army soldiers reported no difference in the incidence of spontaneous abortions among conceptions occurring before and after the Gulf War.¹⁰² However, the incidence of spontaneous abortions among women soldiers was not measured.

A study using birth defects surveillance studies from the six states that conducted active surveillance for birth defects between 1989 to 1993 was recently completed. This data include birth defects measured through the first year of life, accounting for 95 to 99 percent of all birth defects. Further, births in military and nonmilitary hospitals, and to military personnel who have separated from the service are represented. Pilot study data from 17,183 military infants born in Hawaii suggests no difference in birth defects prevalence by parental deployment for any of the 47 birth defects categories.¹⁰³ However, these results require cautious interpretation, pending completion of data analysis in the other states.

TABLE 6
PUBLISHED STUDIES ON GULF WAR VETERAN REPRODUCTIVE HEALTH

Reference	Study design and population	Main outcome measures	Summary of findings
Penman et al. 1996 (100)		Birth defects	Three infants (5.6%) had a major birth defect, similar to rates of other states
Cowan et al. 1997 (101)		Birth defects	No differences in the overall prevalence of major birth defects among GWV infants (7.09%) and NDV infants (7.17%)
Araneta and Moore et al. 1997 (104)		Goldenhar syndrome (oculoauriculovertebral complex)	No statistically significant difference in the prevalence among GWV infants (14.7/100,000) and NDV infants (4.8/100,000)
Goss Gilroy, Inc, 1998 (37)		All health outcomes, including birth defects, stillbirths, spontaneous and induced abortions, low birth weight	Birth defects prevalence was higher among live and stillbirth GWV infants born before, during and after the Gulf War. (Postwar: GWV infants: 6.6%; NDV infants: 2.7%). Spontaneous abortions were more frequent among GWVs (12.3%) than NDVs (9.6%).



TABLE 6

continued

PUBLISHED STUDIES ON GULF WAR VETERAN REPRODUCTIVE HEALTH

Reference	Study design and population	Main outcome measures	Summary of findings
Araneta et al. 2000 (103)		48 selected birth defects	The prevalence of the 48 birth defects were similar for GWV and NDV infants conceived before and after the Gulf War.
Kang et al. 2001 (3.b).		Self-reported birth defects	The risk of veterans reporting birth defects among their children was significantly associated with veterans' military service in the Gulf War. This observation requires confirmation by review of medical records.

GWV= Gulf War veteran; NDV=Nondeployed veteran

In 1995, DoD began an investigation in response to veterans' concerns about a possible excess of the rare birth defect Goldenhar syndrome (oculoauriculovertebral complex — characterized by abnormal prenatal development of facial structures) among Gulf War veterans' infants. Researchers reviewed hospital discharge data from military hospitals to identify infants diagnosed at birth with selected anomalies of the ear, eye, face, jaw and vertebrae.¹⁰⁴ Pediatricians with training in dysmorphology and clinical genetics reviewed medical records from genetics referrals and military and civilian facilities to ascertain cases. Goldenhar syndrome prevalence was 14.7 per 100,000 live births among Gulf War veterans' infants (five case infants /34,069 livebirths) versus 4.8 per 100,000 live births among non-deployed veterans' infants (two case infants /41,345 livebirths), but the difference was not statistically significant and the sample size was too small to enable meaningful statistical comparisons for this rare anomaly.¹⁰⁴

A postal survey of all Canadian Gulf War veterans reported that for 3,113 Canadian Gulf War veterans compared to 3,439 non-deployed veterans, birth defects prevalence was higher for both live and stillborn Gulf War veterans' infants who were born before, during or after the war.³⁷ However, this was based on non-validated, self-reported information, and the types and severity of birth defects were not determined. When stratified by period of conception, the prevalence of birth defects was significantly higher among Gulf War veterans' infants conceived before, during and after the Gulf War compared to non-deployed veterans' infants conceived during similar periods. Birth defects prevalence among prewar conceptions was twice as high among Gulf War veterans' infants (1.5 percent, 33 case infants/2,184 live and still births) than non-deployed veterans' infants (0.74 percent, 19/2,556 live and still births).



This suggests that Gulf War veterans might have had predisposing risk factors for having infants with birth defects before the war. Hospitalization data of Kuwaiti and Bahraini residents showed significant increases of spontaneous abortions during the post-invasion period.^{105, 106}

Although about 50,000 U.S. service women were deployed to the Gulf War, little information is available on their gynecological health. Abnormal uterine bleeding was a common reason for ambulatory visits during the Gulf War.^{107, 108} Postal survey data from Gulf War veterans in Pennsylvania and Hawaii showed no differences in self-reported menstrual problems among Gulf War veterans compared to non-deployed women veterans.³¹ One case series of 16 female Gulf War veterans reported that half experienced gynecologic problems during and after the Gulf War, including irregular menses and uterine fibroids.¹⁰⁹

Air Force women deployed to the Gulf War reported a significant increase of lumps or cysts in the breasts and abnormal Papanicolaou smear results compared to Air Force women deployed elsewhere (35). Finally, evaluation of discharge diagnostic data from military hospitals indicated that women Gulf War veterans had an increased risk of hospitalization after 1991 from genitourinary infections and inflammatory disease of the ovary and fallopian tube.⁴⁰

The prevalence of seminal plasma hypersensitivity, erectile dysfunction, female sexual arousal disorder, dyspareunia and other conditions of sexual dysfunction are unknown among both the general population and military personnel. Published reports on sexual dysfunction among Gulf War veterans are scarce and limited to those reporting symptoms similar to seminal plasma hypersensitivity called "burning semen syndrome."¹¹⁰ Symptoms include penile burning and pain, and localized vaginal burning and pain after seminal contact. Postal survey results from a random stratified sample of U.K. veterans showed a twofold excess of self-reported sexual problems among male Gulf War veterans compared to era controls, and Bosnia conflict veterans.²⁸

Self-reported data from male and female Gulf War veterans in Iowa showed a statistically significant excess of "symptoms of sexual discomfort," compared to non-deployed veterans. Further, female sexual partners of male Gulf War veterans reported more frequent symptoms of sexual discomfort compared to female partners of non-deployed veterans (5 percent vs. 2.4 percent among regular military personnel; 5.4 percent vs. 2.1 percent among National Guard and Reservists).³³



Difficulties in Studying Gulf War Veteran Reproductive Health

Human reproductive health problems are common, but their causes are not well understood. Hazardous exposures may lead to damage to the ova, sperm, zygote or hormonal imbalance prior to conception or during gestation or delivery. Data on miscarriages and spontaneous abortions are incomplete, making it difficult to achieve sufficient statistical power for rare reproductive events, such as congenital anomalies. For example, over 75,000 infants were reviewed in the study of Goldenhar syndrome, but a study involving 250,000 infants would be required to detect a statistically significant difference with sufficient statistical power at the observed birth prevalence for this rare anomaly.

Since national registries of infertility or fetal loss do not exist, case studies or anecdotal information may be all that is available. Moreover, although about 30 percent of biochemically ascertained verified conceptions are terminated spontaneously,¹¹¹ only 10 to 15 percent of fetal losses are clinically recognized.¹¹² Moreover, differences in male and female reproductive biology lead to large differences in susceptibility to environmental reproductive hazards.

These problems make it difficult to establish a link between Gulf War exposures and adverse reproductive outcomes. The absence of birth defects surveillance data among military populations affects most published epidemiological studies, which were necessarily confined to infants born or treated in military hospitals, birth defects diagnosed at birth or limited to small sample sizes. Most of the cohorts consisted of postwar conceptions that did not examine temporal effects or predisposing risks that occurred before the war. Most of these investigations reported all congenital anomalies collectively, which does not facilitate identification of affected organs, individual teratogens, analysis of specific diagnostic groups or opportunities for preventive interventions.¹¹³

The “lesson learned” is the clear necessity of a reproductive health surveillance system for all military personnel. Such surveillance should be capable of prospectively evaluating occupational exposure and collecting clinical data and biochemical markers of hormonal abnormalities, infertility and fetal loss. To this end, on November 1998, the U.S. Assistant Secretary of Defense for Health Affairs established the National Surveillance for Birth Defects.¹²⁴ This surveillance system is intended to be ready in future conflicts and peace-keeping missions to respond to veteran’s concerns about their reproductive health.



Although the Department of Veterans Affairs is solely responsible for the content of this chapter, the following individuals provided invaluable information:

Bradley N. Doebbeling, Department of Internal Medicine, The University of Iowa College of Medicine; Department of Epidemiology, The University of Iowa College of Public Health; and The Iowa City Veterans Affairs Medical Center, Iowa City, IA.

Daniel Clauw, Georgetown Chronic Pain and Fatigue Research Center, Georgetown University Medical Center, Washington, DC.

Drue H. Barrett, Division of Environmental Hazards and Health Effects, National Center for Environmental Health, Centers for Disease Control and Prevention, Atlanta, GA.

Gary D. Gackstetter, The Uniformed Services University of the Health Sciences, Bethesda, MD.

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Han K. Kang, Dr. P.H., The Environmental Epidemiology Service, Department of Veterans Affairs, Washington, DC.

John T. Graham, British Liaison Officer (Gulf Health), Defense Staff, British Embassy, Washington, DC.

Ken C. Scott, Director of Medical Policy, Canadian Forces, Ottawa, Ontario, Canada.

Patricia Doyle, Ph.D., London School of Hygiene and Tropical Medicine, London, England.

Rosario G. Araneta, Ph.D., Naval Health Research Center, San Diego, CA.

Tim A. Bullman, M.S., The Environmental Epidemiology Service, Department of Veterans Affairs, Washington, DC.

William C. Reeves, for the Persian Gulf Veterans Coordinating Board, Division of Viral and Rickettsial Diseases, National Center for Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, GA.



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CHAPTER 4 HEALTH RISK FACTORS

This chapter consists of a discussion of the major health risk factors encountered by many of the men and women who served in the Gulf War. While clinicians and health care providers are the target audience for this chapter, it is written, for the most part, in a non-technical manner so that they may share it with patients who express concerns about these matters. This material also can be found on the VA website: www.va.gov/gulfwar.

4A. Pesticides

Definition

Pesticides are products containing chemicals that are designed to prevent, destroy, repel or reduce pests. In the United States, pesticides are regulated by the U.S. Environmental Protection Agency (EPA). The EPA is charged with evaluating pesticides before they can be marketed and used in the United States to ensure that they will not pose unreasonable adverse effects to human health and the environment. EPA grants those pesticides that meet their requirements a “registration” or license permitting their distribution, sale and use. In general, pesticides are regulated and licensed for specific uses, such as with a specific crop, by licensed applicators. Some pesticides are considered sufficiently safe to be licensed for essentially unrestricted use for home and personal protection.

In 1991 during the Gulf War, DoD shipped a variety of pesticides to protect U.S. service members from endemic pests. These included carbaryl (Sevin®), chlorpyrifos (Dursban®), DEET (for example OFF® and Cutters®), diazanon, dichlorvos (Vapona®), lindane, malathion, methomyl (Lannate®), permethrin, propoxur (Baygon®), pyrethroids and rodenticide baits (1996 PAC Final Report). These items represent four major pesticide categories, including organophosphorus (OP), methyl carbamate (MC), organochlorine (i.e., lindane) and pyrethroid (e.g., permethrin). The insect repellent DEET is unique in that it is not part of a broader chemical class of pesticides.

All of these specific products were each registered by the EPA for general, unrestricted use by private citizens in the United States. EPA made this determination based upon scientific studies demonstrating that these pesticides can be used without posing unreasonable risks to people or the environment. In fact, all of these pesticides were widely available in 1991 at home and garden shops in the United States. Most are still available today. However, one pesticide, chlorpyrifos, was removed from general household use by the EPA in June 2000 based on health risk concerns, particularly to exposed children. There have been anec-



total reports of pesticides that may have been purchased locally in the Gulf War theater. The potential significance of these anecdotes is difficult to evaluate today, nearly 10 years after the Gulf War, and are not considered here.

How Gulf War Veterans were Exposed

U.S. service members may have been exposed to any of the pesticides shipped to the Gulf during the Gulf War in the same manner that civilians in the U.S. may be exposed. Even careful conventional use of these pesticides will result in some small exposure to those using the products or those in the immediate vicinity. Most of these products are used as sprays, which can result in exposure from inhalation of vapors or from skin contact and absorption. Contrary to some reports, military clothing was not pretreated with insect repellents prior to shipment.

According to DoD policy at the time of the Gulf War, most U.S. service members had access only to permethrin in a spray can for treating clothing, and DEET liquid or stick for personal protection against mosquitoes and flies. Unrestricted use or even potential misuse of those two pesticides would have resulted in exposure by those using the materials and possibly those in the immediate vicinity where they were used.

According to DoD, all the other pesticides shipped to the Gulf War were to be used only by specifically trained personnel, or for special applications. For example, lindane was reportedly used only for treating Iraqi prisoners of war as a delousing agent [Presidential Advisory Committee (PAC), Final Report]. Other pesticides were used for sanitation or insect control purposes (e.g., malathion and Dursban) at military facilities. Personnel involved with applying these materials and those in the immediate vicinity would have had some exposure to them, although exposure levels under these controlled conditions presumably would be quite small. Although there were anecdotal reports of unauthorized use of locally obtained pesticides, this has been difficult to confirm or evaluate.

How Pesticides Enter/Leave the Body

Most of these pesticides are applied as sprays. Any material used as a spray can enter the body through breathing the aerosolized and vapor form of the material. DEET applied as a liquid or stick to the skin can enter the body by absorption through the skin. Most Gulf War service members would be most likely to have pesticides enter their bodies through accidental breathing of vapors produced from spray application of the insecticide, but absorption from skin contact during application operations also may have occurred. In general, once these pesticides enter the body, they are quickly metabolized (broken down) in the body



and excreted in urine and feces. Their rapid metabolism and excretion from the body is one reason why this group of pesticides is considered to be sufficiently safe for unrestricted use in the United States. Lindane, the only organochlorine pesticide in this group, is metabolized and excreted relatively more slowly (ATSDR).

Health Effects of Pesticides

As a class, the organophosphorus (OP) pesticides cause inhibition of the enzyme acetylcholine esterase (AChE). This enzyme is crucial to normal nerve and nerve/muscle functioning. Inhibition of AChE is essentially irreversible and complete recovery involves the body's production of new enzyme over a period of days or weeks. Thus, acute (immediate) cholinergic poisoning symptoms usually develop within hours of exposure and include miosis, headache, nausea, dizziness, anxiety and restlessness. Life-threatening symptoms from acute cholinergic poisoning may include muscle fasciculation, weakness, tremor, uncoordination, vomiting, abdominal cramps, diarrhea, sweating, salivation and excessive tearing, and death can occur by respiratory paralysis. Acute cholinergic poisoning by more toxic OP pesticides is a serious health risk. Recently, the EPA restricted the use of Dursban, one of the OP pesticides used in the Gulf War, to trained applicators only, based upon concerns about unacceptable acute toxicity risks. Previously, and during the Gulf War, Dursban had been approved for unrestricted home use.

Some patients who survive severe acute OP poisoning show subtle, chronic neurological abnormalities that can be detected using standardized neurological tests. These effects can remain for months or years, following the acute poisoning event. For example, subtle deficiencies are reported for survivors of acute OP poisoning in tests for intellectual functioning, academic skills, abstraction and flexibility of thinking and simple motor skills. However, according to DoD, in-theater medical personnel did not report any acute symptoms in Gulf War service personnel consistent with acute cholinergic poisoning that would be caused by either OP pesticides or related chemical warfare agents. Although a few OP pesticides are known to cause delayed neuropathies (or polyneuropathies) following recovery from acute cholinergic poisoning, none of the OP pesticides used in the Gulf War are considered to cause such effects under any conceivable usage.

The methyl carbamate (MC) pesticides cause reversible inhibition of the enzyme AChE, and acute poisoning results in symptoms that are very similar to that seen with OP pesticides, but with shorter duration. Acute MC poisoning has not been associated with chronic neurologic effects.

Permethrin has very low human toxicity. This is a major reason why it is licensed by EPA for unrestricted use in personal care products such as shampoos and lotions, or for treating clothing. There are few reported human poisonings from this pesticide. Similarly, lindane



has very low acute toxicity, although at extremely high exposures it has been reported to cause liver and kidney damage. Lindane is reported to cause liver cancer in laboratory animals, and therefore, may be a carcinogen.

DEET, introduced as an insect repellent in the 1950s, remains widely used in the United States today in brands such as OFF and Cutters. According to EPA, there are 225 DEET registered repellent products to be applied directly to the skin and clothing in various forms, including aerosol and non-aerosol sprays, creams, lotions, sticks, foams and towelettes. DEET generally is of low acute toxicity, and based upon the available toxicological data, the EPA reports that the normal use of DEET does not present a health concern to the general U.S. population.

Although DEET's use has been implicated in causing seizures among children, the EPA reports that the data are insufficient to establish DEET as the cause of the reported effects. However, because of DEET's unusual use pattern (direct application to human skin and clothing) and its possible association with seizure incidents, the EPA considers it prudent to require clear, common sense directions for use and improved label warnings with restrictions on all DEET product labels.

Effects on Children

In general, EPA requires information from manufacturers demonstrating a pesticide does not cause birth defects or other reproductive and developmental toxic effects to allow licensing for unrestricted general use by the American public. Moreover, as pesticide classes, the OP, MC, permethrin and DEET are not considered to be teratogenic in laboratory animals. However, pregnant rats fed the maximum tolerated dose of lindane showed a statistical increase in teratogenic effects in offspring. The greatest concern for teratogenic compounds is potential exposure to a developing fetus via exposure to the mother. The risk of birth defects in children of men who were exposed prior to conception of the child is clearly much lower.

Finally, it seems likely that overall pesticide exposure by U.S. service members during the Gulf War would have been similar to pesticide exposure to a similar group of U.S. civilians who remained in the United States. Thus, it appears unlikely that birth defects in offspring of Gulf War veterans are related to pesticide exposures that occurred during the Gulf War.



No Available Test for Pesticide Exposure

All of these pesticides, including the organochlorine agent lindane, are rapidly metabolized and excreted following exposure. Therefore, there is no test available today that can detect an exposure to any of these pesticides that may have occurred in 1991. Furthermore, all these pesticides are widely used within the United States, and essentially all Americans might have some exposure. Consequently, even if a test for exposure were available, it would be difficult to distinguish exposures that may have occurred during the Gulf War from exposures that may have occurred after returning to the United States.



Findings from Scientific Reviews

Several scientific review committees also have reviewed the health consequences of possible exposure to pesticides by U.S. service members during the Gulf War. The Presidential Advisory Committee on Gulf War Veterans' Illness concluded in its 1996 report that "it is unlikely that health effects and symptoms reported today by Gulf War veterans are the result of exposures to pesticides during the Gulf War." It also found that it is too early to detect any potential carcinogenic effects in Gulf War veterans that could be due to exposure to the carcinogen, lindane, even if they were to occur.

The 1996 Institute of Medicine report concluded that "[in] general, it appears that the average personal usage of the pesticides available in the Persian Gulf War theater of operations was low and unlikely to be associated with induction of chronic disease." In addition to these reports, the 1994 National Institute of Health Technology Assessment Workshop Statement concluded that "chronic responses to OP are considered unlikely because of the absence of reported polyneuropathies among the examined veterans." A more indepth review of the health risks of pesticides is being done at the IOM. It should be completed in September 2002.

Lastly, the 1994 Defense Science Board report concluded ". . . there were no reports of acute pesticide poisoning during the war. If continued analysis of the VA registry indicates a higher incidence of neurophysical disorders in those veterans whose duties included routine application of pesticides, pesticide exposure may come under closer scrutiny as an etiological



factor for other participants.”



More Information

Additional information can be obtained from:

Pesticides and Related Compounds, McConnell, R., in Textbook of Clinical Occupational and Environmental Medicine, L. Rosenstock and M.R. Cullen, eds., 1994, W.B. Saunders.

Toxic Effects of Pesticides, Ecobichon, D.J., in Casarett & Doull's Toxicology: The Basic Science of Poisons, C.D. Klaassen ed., 5th edition 1996, McGraw-Hill.

U.S. Department of Health and Human Services, Agency for Toxic Substances and Disease Registry, Frequently Asked Questions About Contaminants Found at Hazardous Waste Sites, <http://www.atsdr.cdc.gov/toxfaq.html>

U.S. Environmental Protection Agency (EPA) Office of Pesticide Programs (OPP) website <http://www.epa.gov/pesticides/>

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4B. Chemical and Biological Warfare Agents

Definition

Chemical and biological warfare agents are materials that are deliberately designed to cause lethal and debilitating toxic effects or acute infectious disease in humans. In the last decades, the most common chemical warfare agents of concern include organophosphorus (OP) nerve agents such as sarin, soman and/or VX, and vesicant (blistering) agents such as mustard agent. Biological warfare agents include aerosolized active spores of anthrax (*Bacillus anthracis*), and botulinum toxin, a potent nerve toxin protein isolated from fermentation of the commonly occurring bacterium *Clostridium botulinum*.

The OP nerve agents have a chemistry and a cholinergic mode-of-action very similar to the OP pesticides, but are designed to be more toxic to humans. Anthrax infection most commonly occurs naturally in farm animals but also is found in humans through contact with infected animals or by inhalation of spores from infected animal products, such as hides. Botulism poisoning also occurs naturally in humans, for example, through exposure to the toxin formed by bacteria in contaminated food. Botulinum toxin is considered a biological weapon because of its biological origin, although as a toxin it does not multiply or reproduce in the manner of a bacterial organism.

Iraq was known to possess both chemical and biological weapons. However, the U.S. Department of Defense (DoD) has reported that neither chemical nor biological weapons were intentionally used by Iraqi forces against coalition forces during the Gulf War. DoD has confirmed that one U.S. soldier received a burn from mustard agent (on his arm), caused by accidental exposure while exploring a captured bunker in southern Iraq. The British Ministry of Defense also has concluded that neither chemical nor biological agents were used by Iraqi forces during the Gulf War.



Gulf War Veterans' Exposure

Some Gulf War veterans may have been exposed to trace levels of chemical warfare agents. In March 1991, following the end of the Gulf War, U.S. service members used explosives to destroy a large ammunition depot in southern Iraq, known as Khamisiyah. This site was later found to have contained chemical agent munitions including sarin and the closely related agent cyclosarin. Some amounts of these agents were released into the atmosphere during demolition. Based upon atmospheric transport modeling carried out by the CIA, in 1997 DoD notified nearly 100,000 Gulf War veterans who had been in the vicinity of Khamisiyah at the time of the demolitions that they could have been exposed to low-levels of these chemical agents, which would have been too low to cause any acute cholinergic poison signs and symptoms.

Although the exact levels of exposure have been estimated to be very low or trace, DoD has stated that no cases of acute cholinergic poisoning symptoms related to exposure to OP nerve agents were reported during the Gulf War. Nevertheless, low-level (asymptomatic) exposures from inhalation may have occurred to some U.S. service members in the Gulf War region in the days following the cease-fire in 1991.

Methods of Exposure

Chemical warfare agents can be absorbed either by inhalation of vapors or through dermal contact. Sarin and cyclosarin are relatively volatile agents, and the primary exposure concern for these agents is via inhalation. Mustard agent is much less volatile, and the primary exposure is dermal contact, although inhalation of aerosolized mustard agent also can be an important route of exposure. All of these chemical warfare agents are rapidly metabolized and excreted, primarily in the urine, following any route of exposure.

Anthrax infection can occur through inhalation, cutaneous exposure and gastrointestinal exposure. Naturally occurring anthrax infection is usually through cutaneous exposure and most commonly occurs in farm animals. Anthrax exposure for weaponized material is through inhalation exposure from aerosolized spores. Inhalation leads to pulmonary anthrax infection, which is normally a rare form of this disease, compared to cutaneous anthrax infection. Gastrointestinal anthrax infection also is a rare form of this disease, except in specific outbreaks. Pulmonary infection resulting from a minimal amount of spores leading to interaction can increase the incubation time of the disease, but nevertheless, such an infection can ultimately progress to a full-blown case and usually death, unless treated early.



Health Effects

Botulinum toxins are proteins that rapidly break down in the environment following aerosolizing from weapons. Botulinum toxins that have been absorbed by the body, on the other hand, can cause physiological effects for days or even weeks, following exposure.

The OP chemical warfare agents cause symptoms that are virtually identical to those caused by OP pesticides. These agents cause inhibition of the enzyme acetylcholine esterase (AChE), which is crucial to normal nerve and nerve/muscle functioning. The inhibition is irreversible, and complete recovery involves the body's production of new enzymes. Acute cholinergic poisoning symptoms usually develop within hours of exposure and include miosis, headache, nausea, dizziness, anxiety and restlessness. Life-threatening symptoms may include muscle fasciculation, weakness, tremor, uncoordination, vomiting, abdominal cramps, diarrhea, sweating, salivation and excessive tearing; death can occur by respiratory paralysis.

According to DoD, in-theater medical personnel did not report any acute symptoms in Gulf War service personnel consistent with acute poisoning from these chemical warfare agents. This is significant, because some patients surviving severe OP poisoning later go on to develop subtle, chronic neurological abnormalities that can be detected using standardized neurological tests. For example, subtle deficiencies are reported for survivors of acute OP poisoning in tests for intellectual functioning, academic skills, abstraction and flexibility of thinking and simple motor skills. Although certain OP chemicals are known to cause delayed neuropathies (or polyneuropathies) following recovery from acute cholinergic poisoning, the OP chemical warfare agents as a class are not considered to cause such effects.

Exposure to mustard agent can cause severe irritation and tissue damage, including typical blistering to eyes, skin, respiratory and gastrointestinal tracks. Signs and symptoms from mustard agent are delayed for some hours following exposure. The mustard agent is considered to be a likely human carcinogen, and humans exposed to mustard agent are at increased risk of respiratory, skin cancers, leukemia and other disorders decades following exposure.

Anthrax spores following inhalation are transported via the lymph system to mediastinal lymph nodes, where they can germinate up to 60 days later (but usually within a few days). Following germination, clinical manifestations occur rapidly as replicating bacteria release toxins leading to hemorrhage, edema and necrosis. Pulmonary anthrax infection almost always has been fatal, even with antibiotic treatment, once symptoms have begun.



Botulinum toxin blocks neuromuscular conduction by binding to receptor sites on the motor nerve terminals and by inhibiting the release of the neurotransmitter acetylcholine. Symptoms can include respiratory distress and respiratory paralysis, and death can occur by suffocation. There are no long-term health effects reported in individuals surviving pulmonary anthrax infection. Some individuals surviving botulism poisoning from contaminated food or other natural sources experience residual weakness for as long as a year after disease onset.

Effects on Children

OP nerve agents, including pesticides and chemical warfare agents, are not considered to be teratogenic agents. Mustard agent is considered to be a likely human carcinogen, but current information is not sufficient to conclude that it has human reproductive health effects, especially following exposure in males.

Pulmonary anthrax almost always is fatal if not treated with antibiotics before onset of symptoms, but there is no reason to expect individuals surviving anthrax infection to be at increased risk for adverse reproductive health effects.

Botulinum toxin (in a purified form and at low doses) is actually licensed by the FDA for therapeutic uses as Botox®. Botulinum toxin is not considered a teratogenic agent.

Testing

OP and mustard chemical weapon nerve and blister agents are rapidly metabolized and excreted, and metabolites indicating exposure can be detected in urine in hours following exposure. But metabolism and excretion of these compounds will be complete within days of an exposure in cases where the individual survives the initial exposure. Consequently, there is no test available today that can confirm exposure to these chemical warfare agents that may have occurred several months or years in the past.

In principle, it should be possible to detect antibodies to anthrax in individuals exposed to anthrax bacillus, but who did not develop the disease. However, there is no commonly available test for detecting exposure to anthrax bacteria at levels that did not cause actual clinical manifestations of infection. Exposure to botulinum toxin proteins at subacute doses may cause an immunological response, but there is no conventional test for subclinical exposures that may have occurred months or years in the past.



Findings from Scientific Reviews

The Presidential Advisory Committee on Gulf War Veterans' Illnesses (PAC) concluded in its 1996 report that "based on available data, it is unlikely the health effects reported by Gulf War veterans today are the result of exposure to OP or mustard CW agents during the Gulf War." Relative to biological warfare agents, the PAC concluded that "it is unlikely the health effects reported today by Gulf War veterans are the result of exposures to BW agents." The PAC cautioned that aflatoxin, another suspected biological warfare agent, could cause increased cancer in veterans in the decades following the Gulf War, although according to DoD, aflatoxin was not used by Iraq during the war. The Defense Science Board Task Force on Persian Gulf War Health Effects (DSB) concluded in its 1994 report that "... there is no indication from research that there would be chronic sequelae from low level exposure even if it had occurred."

Relative to biological agents, the DSB concluded, "The diseases associated with BW agents, e.g., anthrax, botulinum, etc., are notable for acute effects and would have been rapidly evident and readily diagnosed had they occurred among U.S. or coalition troops during the war." The Institute of Medicine 1996 report "Health Consequences of Service During the Persian Gulf War" (IOM) concluded "... there is no available evidence in human or animal studies to date that exposure to nerve agents at low levels produce any detectable acute clinical or physiological manifestations results in any chronic or long-term adverse health effects."

Nevertheless, it is important to note that all of these independent review groups caution that we do not have a great deal of information on which to base conclusions about long-term effects of exposure to low-levels of chemical or biological warfare agents, and that further research may be justified.

More Information

Many of the sources mentioned in the section on health effects from OP pesticides also are highly relevant to our understanding of health effects from chemical warfare agents. Also see:

Anthrax as a Biological Weapon: Medical and Public Health Management, *Journal of the American Medical Association*, Consensus Statement, May 12, 1999, 281(18) 1735 — 1745.



Review of health consequences from high-, intermediate- and low-level exposure to organophosphorus nerve agents, Mark A. Brown and Kelley A. Brix, 1998. *Journal of Applied Toxicology*, 18(6), 393-408.

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Report of the Defense Science Board Task Force on Persian Gulf War Health Effects, Office of the Under Secretary of Defense for Acquisition and Technology, Washington, DC, 1994.



4C. Vaccinations and Pretreatments

Vaccinations

Before deployment in the Gulf War, all U.S. troops were given the standard series of inoculations against infectious diseases that would be provided to any U.S. citizen traveling to that part of the world.

Concerns about Iraqi offensive biological warfare capabilities resulted in a decision to use available vaccines as preventive measures against these agents. After their arrival in the theater of operations, some Gulf War participants received an additional two nonlive vaccines for protection against two biological warfare agents — anthrax and botulinum toxoid.

It has been estimated that about 8,000 troops received the botulinum vaccine, but the Food and Drug Administration (FDA)-approved anthrax was administered to a much larger population of about 150,000. Unfortunately, medical records from the Gulf War contain little or no information about who received these vaccines, when and how often the vaccines were given to the troops, or the timing relative to other exposures.

Concerns have been expressed about the possible long-term health consequences of these vaccines alone or in combination with other agents. A number of studies have been approved and are underway to consider this hypothesis.

Anthrax Vaccine

In humans, the principal use of this vaccine was for the protection of occupationally exposed individuals. Protective antigen is the immunogenic component of both the U.S. and the U.K. vaccine. It is unknown how many individuals actually received the vaccine in the theater of operations in Southwest Asia. In December 1997, the Secretary of Defense ordered that U.S. military service members receive the anthrax vaccination for their protection against the threat of biological warfare.

Health Effects of Anthrax Vaccine

There is little published, peer-reviewed literature on the possible long-term health consequences of exposure to the anthrax vaccine. In a clinical trial of workers exposed occupationally, there were no reports of adverse effects beyond 48 hours after each vaccination. (Brachman et al., 1962).

A common reaction is described as a ring of erythema (1–2 cm in diameter) at the injection



site, with local tenderness that lasted 24–48 hours. Some subjects reported more extensive edema, erythema (more than 5 cm in diameter), pruritus, induration or small painless nodules at the injection site (lasting up to several weeks). Twenty-one individuals had moderate local edema that lasted up to 48 hours.

The only systemic reactions were reported in two individuals (0.9 percent of the actively vaccinated subjects) who experienced “malaise” lasting 24 hours following vaccination. The study notes that three individuals who received the placebo (0.1 percent alum) had mild reactions. However, studies of the anthrax vaccine have not used active surveillance to systematically evaluate long-term health outcomes. Unfortunately, this situation is typical for all but a few vaccines.

IOM Conclusions about the Health Risks of the Anthrax Vaccine

In its report, entitled *Gulf War and Health: Volume 1. Depleted Uranium, Sarin, Pyridostigmine Bromide and Vaccines*, the National Academy of Sciences' Institute of Medicine concluded that:

- there is sufficient evidence of an association between anthrax vaccination and transient acute local and systemic effects (e.g., redness, swelling and fever), as is typically associated with vaccination; and
- there is inadequate/insufficient evidence to determine whether an association does or does not exist between anthrax vaccination and long-term, adverse health effects.

Botulinum Toxoid Vaccine

Botulinum toxins, best known for cases of foodborne botulism, are produced by the bacterium *Clostridium botulinum*. Different strains produce seven different, distinct botulinum toxins, which are among the most toxic compounds. Efforts to change the botulinum toxin to the nontoxic form of a toxoid date back more than 75 years.

The current botulinum toxoid vaccine is classified as an “Investigational New Drug” by the Food and Drug Administration. The vaccine has been tested on volunteers and used for occupationally at-risk workers. It is administered at zero, two, and 12 weeks, followed by annual boosters. Recent advances have opened up avenues for new botulinum vaccine development.



Health Effects of Botulinum Toxoid Vaccine

Early studies of the initial toxoids (in the 1940's) found a significant number of local and systemic reactions. Later research that focused on the efficacy of the vaccine noted moderate local or systemic reactions. Studies of the vaccine have not used active surveillance to systematically evaluate long-term health consequences.

IOM Conclusions about the Health Risks of the Botulinum Toxoid Vaccine

In its report, entitled *Gulf War and Health: Volume 1. Depleted Uranium, Sarin, Pyridostigmine Bromide and Vaccines*, the National Academy of Sciences' Institute of Medicine concluded that:

- there is sufficient evidence of an association between botulinum toxoid vaccination and transient acute local and systemic effects (e.g., redness, swelling and fever), as is typically associated with vaccination; and
- there is inadequate/insufficient evidence to determine whether an association does or does not exist between botulinum toxoid vaccination and long-term, adverse health effects.

Multiple Vaccinations

Military personnel often receive several vaccinations as they prepare for service in an environment with many endemic diseases. Some vaccinations are administered routinely to all military recruits; others are administered for deployment to specific geographic or high-risk areas; and still others are specific to the occupational setting. People have expressed concerns that multiple vaccinations prior to and during Gulf War service may have caused adverse health effects.

Health Effects of Multiple Vaccinations

Certain multiple vaccination regimens can lead to suboptimal antibody responses, but there is little evidence, largely because of a lack of active monitoring, of adverse clinical or laboratory consequences beyond the transient local and systemic effects seen frequently with any vaccination.



A group of 99 employees at Fort Detrick, Maryland, who received many vaccinations related to occupational requirements, were followed for up to 25 years to investigate the potential subclinical effects of intensive vaccination. The participants underwent physical examinations and laboratory testing in 1956, 1962 and 1971 (Peeler et al., 1958, 1965; White et al., 1974). No clinical sequelae attributable to intense, long-term immunization could be identified in this cohort. None of the subjects suffered unexplained clinical symptoms, requiring them to take sick leave, that could be attributed to the vaccination program.



There was some evidence of a chronic inflammatory response, as characterized by certain laboratory test abnormalities. However, these changes cannot necessarily be attributed to the vaccinations, because the workers studied were occupationally exposed to a number of virulent microbes. This series of longitudinal clinical studies had several shortcomings. However, the studies were valuable because careful monitoring did not disclose any evidence of serious, unexplained illness in a cohort that received a series of intense vaccination protocols over many years.

Several studies of U.K. Gulf War veterans provide some limited evidence of an association between multiple vaccinations and long-term multisymptom outcomes, particularly for vaccinations given during deployment (Unwin et al., 1999; Hotopf et al., 2000). There are some limitations and confounding factors in these studies, and further research is needed.

IOM Conclusions about the Health Risks of Multiple Vaccinations

In its report, entitled *Gulf War and Health: Volume 1. Depleted Uranium, Sarin, Pyridostigmine Bromide and Vaccines*, the National Academy of Sciences' Institute of Medicine concluded that there is inadequate/insufficient evidence to determine whether an association does or does not exist between multiple vaccinations and long-term, adverse



health effects.

Pyridostigmine Bromide (PB)

Pyridostigmine bromide was a drug used in the Gulf War as a pretreatment for exposure to nerve agents. PB, approved by the FDA in 1955, has been used for decades in anesthesia and for the treatment of a neuromuscular disease (myasthenia gravis). In the treatment of myasthenia gravis, the average dose is 120-600 mg per day (in divided doses). The size and frequency must be adjusted for individual patients. PB is poorly absorbed after oral administration; peak plasma levels occur two or three hours after administration. It is eliminated almost exclusively in the urine.

The FDA classified PB as an “investigational new drug” for the purpose of chemical warfare pretreatment. Furthermore, the FDA waived informed consent for its use to make the best medical treatment available in a specific combat situation.

PB in the Gulf War

PB was disseminated in packets containing 21-thirty mg. tablets. When commanders determined that the risk of chemical attack was significant, the tablets were self-administered by troops — one tablet every eight hours for up to a week. The Department of Defense reported that 5.3 million doses were sent to the theater of operations and that about 250 thousand troops took PB at least once.

Health Effects of PB

Adverse side effects of PB are generally related to the large doses given to myasthenia patients. Problems noted include nausea, vomiting, diarrhea, abnormal cramps, increased peristalsis, increased salivation, increased bronchial secretions, miosis, heavy perspiration, fasciculations and weakness.

PB often produced mild, acute gastrointestinal and urinary problems among Gulf War participants. These problems generally were observed within hours of taking the initial tablet. In many instances, these effects subsided after a day or two. In other troops, the problems continued as long as the PB tablets were taken. Some troops took PB with meals to minimize gastrointestinal symptoms. Less than one percent of U.S. troops in the Gulf War required a medical visit after taking PB. Fewer than one-tenth of one percent were advised by medical personnel to discontinue use of PB.



What Reviewers have Concluded

Several independent scientific committees have reviewed the medical and scientific literature on Gulf War health exposures and have not ruled out the possibility of long-term health effects from taking this drug. These reviews, conducted by teams of scientists, physicians, public health specialists and others, include the 1994 "NIH Technology Assessment Workshop," the 1996 Institute of Medicine "Report of the Committee to Review the Health Consequences of Service During the Persian Gulf War," the 1996 "Presidential Advisory Committee on Gulf War Veterans' Illnesses," the 1998 "Report of the Special Investigation Unit on Gulf War Illnesses" and the 1999 "Rand Report on PB."



Combined Effects

Concerns have been expressed about the possibility of increased health problems from PB when it is combined with other possible risk factors or exposures. Some researchers suggest that PB in combination with stress may affect the central nervous system. The insect repellent DEET and the insecticide permethrin have been mentioned as risk factors when used in conjunction with PB. Animal studies have suggested that PB may result in increased toxicity in combination with pesticides. Researchers are exploring these possibilities.

IOM Conclusions about the Health Effects of PB

In its report, entitled *Gulf War and Health: Volume 1. Depleted Uranium, Sarin, Pyridostigmine Bromide and Vaccines*, the National Academy of Sciences' Institute of Medicine concluded that there is inadequate/insufficient evidence to determine whether an association does or does not exist between PB and long-term, adverse health effects.

More Information

For additional information regarding vaccines and PB, see the IOM report cited above, plus references listed below.

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4D. Depleted Uranium

Definition

Depleted uranium (DU)

is a by-product of the uranium enrichment process. The refining and processing of uranium ore involves separating the isotopes U-235 and U-238 to form enriched uranium for use in nuclear reactors and nuclear weapons.

DU is the metal residue remaining after the enrichment process is completed. DU possesses less U-235 and about 50 percent of the radioactivity of natural uranium and is used commercially in medicine for radiation shields, in aviation as counterweights, in petroleum exploration as drilling equipment and in space as satellite ballast. Because of its density, availability and cost, the U.S. Military and those of other countries use DU in both armor-piercing projectiles and in armor.

Natural and depleted uranium differ only in their radioactivity, with DU being half as radioactive. The various isotopes of uranium are primarily alpha emitters. Alpha particles travel only 30 micrometers in skin and cannot penetrate glass, dead skin or paper. Therefore, DU is classified as a low-level radioactive material.

The chemical properties of uranium and DU, however, are the same. Uranium is classified as a heavy metal similar to tungsten, lead and mercury. Its chemical properties and specifically heavy metal toxicity that are the primary causes for concern about the possible health effects from DU exposure.



How Veterans were Exposed

When a vehicle is hit and penetrated by a DU projectile, the projectile splits into small shards and bursts into flames. The projectile fragmentation may fill the vehicle with flying metal fragments, particles and dust. Soldiers in the vehicles may inhale or swallow airborne particles, be injured by fragments or have wounds contaminated by DU fragments, particles and dust. Soldiers can have retained shrapnel imbedded in soft tissue and muscle. The largest pieces of shrapnel are removed when possible, but some shrapnel particles are too small to be safely removed without doing damage to the surrounding tissue. Rescuers who entered vehicles damaged by DU projectiles also may be exposed to dust and airborne particles. Other veterans may be exposed to DU dust and particles during salvage, cleaning and reclamation operations.

How DU Enters the Body

In non-military situations, the main routes of uranium uptake by the human body are inhalation and ingestion, as is the case with other heavy metals. In the military environment, additional routes of uranium exposure exist, such as from embedded metal fragments slowly dissolving in the body and uranium-contaminated wounds. All of these routes of internalization contribute to the total body burden of uranium.

Outside the military and industrial settings, the major portion of the natural body burden of uranium for a typical civilian is derived from ingested and inhaled material. There is natural uranium in the air, food and water. The origin of the uranium may be natural or it may be from man-made sources, such as uranium in phosphate fertilizer or the fossil fuels.

Health Effects of DU

The health effects of DU exposure are related not only to the presence of uranium, but also to the amount and duration of the exposure. The two major health concerns from exposure to DU are radiation and heavy metal toxicity.

External radiation exposures, that is, when DU is not taken into the body, result in minimal radiation exposure. Concerns about internal radiation exposure should be tempered by the knowledge that DU is much less radioactive than naturally occurring uranium.

The primary health concern with DU exposure is heavy metal toxicity, and the primary target for DU toxicity is the kidney.





What Review Groups and Studies have Concluded about DU Risks

Research into the health effects of DU exposure has been limited. Until recently, there have been no published studies of soldiers exposed to DU in wartime. Most of the knowledge about the effects of uranium on humans has been from studies of uranium miners and millers. These studies are not generally relevant to DU-exposed veterans.

Uranium miners and millers have been exposed to uranium as well as radon and other substances present in mines. Also, miners and millers are exposed to these substances in larger quantities and for longer periods. The studies of the health effects of uranium exposure on uranium miners have shown a potential for a radiologic lung hazard from breathing uranium dust for extended periods. Studies also have found an increased incidence of lung cancer, but that is thought to be from a combination of uranium and radon exposure.

Other studies have shown an increased risk of kidney problems in animals and humans exposed to uranium for extended periods.

Health Surveillance

Currently, the Department of Veterans Affairs (VA) is following approximately 50 veterans who were injured during friendly fire incidents during the Gulf War. So far, only a few health effects have been observed. Soldiers with embedded DU shrapnel fragments have higher than expected urine uranium levels. Also, subtle changes in neuropsychological tests results have been observed in some individuals. Most soldiers in the study have some problems associated with the injuries sustained during combat, but otherwise are indistinguishable from other soldiers who were not in the Gulf War. One other blood measure of a hormone (prolactin) is elevated at the group level, but does not appear to be of clinical significance or to have caused a change in sexual function.

Among the families of the 50 veterans currently enrolled in the VA DU program, there have been approximately 20 births since the veterans' return from the Gulf War, with no known birth defects. Also as noted above, the hormone prolactin level is elevated in some individuals, but does not appear to be of clinical significance or to have caused a change in sexual function. However, given the known effects of other heavy metals on reproductive health and the evidence supporting the biological plausibility, further study is warranted.



DU Test*

Isotopic analysis is a test that can be used to detect depleted uranium. In contrast, a 24-hour urine test measures only total uranium. A total urine uranium count, however, includes DU plus any natural uranium from food or water that an individual consumes. The chemical properties of uranium that affect health are related to systemic levels of total uranium. Total uranium can be measured by the total urinary uranium concentration in a 24-hour period. If the amount of uranium in the urine exceeds the amounts expected from natural sources, an isotopic analysis can be done to determine if DU is present.

Isotopic analysis is the measurement of the different components or isotopes of uranium. The three isotopes of uranium occur in different proportions in natural and depleted uranium.

Gulf War veterans who think that they have health problems attributable to their service in the Gulf War and possible exposure to DU should contact their nearest VA Medical Center for a Gulf War Registry Examination and, if necessary, a 24-hour urine uranium screening.

Veterans with a disability or health problem possibly related to their Gulf War service are encouraged to file a claim for disability compensation. A veterans' benefits counselor at the nearest VA Regional Office can provide assistance and information. The toll free number for claims assistance is 1-800-827-1000.

The Baltimore DU program is coordinating urine uranium testing for the VA. Veterans concerned about the possible health consequences of DU exposure are encouraged to contact the most convenient VA Medical Center for a DU screening.

The Baltimore Depleted Uranium Program staff also is available for consultation with primary care physicians on DU-related issues. In particular, the DU program staff have a unique expertise and are available for assistance with general information about DU exposures, determination of possible exposures, assessment of risk, guidance with selecting appropriate medical tests, obtaining and interpreting urine uranium test results, counseling advice and referral to other specialists.

* Follow-up testing has shown improvements in neurocognitive test results and prolactin levels.



Recent IOM Findings

In its report released in September 2000, titled *Gulf War and Health: Volume 1. Depleted Uranium, Sarin, Pyridostigmine Bromide and Vaccines*, the National Academy of Sciences' Institute of Medicine concluded that:

- there is limited/suggestive evidence of no association between exposure to uranium and lung cancer at cumulative internal dose levels lower than 200 mSv or 25 cGy;
- there is inadequate/insufficient evidence to determine whether an association exists between exposure to uranium and lung cancer at higher levels of cumulative exposure;
- there is limited/suggestive evidence of no association between exposure to uranium and clinically significant renal dysfunction; and
- there is inadequate/insufficient evidence to determine whether an association exists between exposure to uranium and the following health outcomes: lymphatic cancer; bone cancer; nervous system disease; nonmalignant respiratory disease; or other health outcomes (gastrointestinal disease, immune-mediated disease, effects on hematological



parameters, reproductive or developmental dysfunction, genotoxic effects, cardiovascular effects, hepatic disease, dermal effects, ocular effects or musculoskeletal effects).

More Information

More information about depleted uranium can be found in the four Depleted Uranium Fact Sheets and the FAQ Sheet produced by the Baltimore VAMC Depleted Uranium Program staff. These cover the DU program in more detail and address frequently-asked veterans' questions.

Physicians also are encouraged to refer to some recent studies published by the Baltimore DU Program and others as excellent sources of information about veterans exposed to DU. Some citations are provided below:

Determination of the Isotopic Composition of Uranium in Urine by Inductively Coupled Plasma Mass Spectrometry. J.W. Ejniak et. al., Health Phys. 78(2): 143-146; 2000.

Health Effects of Depleted Uranium on Exposed Gulf War Veterans. McDiarmid et. al., Environmental Research, February 2000.

Elevated Urine Uranium Excretion by Soldiers with Retained Uranium Shrapnel. Hooper et. al, Health Physics, November 1999.

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4E. Infectious Diseases

Based on high rates of illness among Allied troops sent to the Persian Gulf during World War II, Gulf War troops were expected to be at increased risk of sandfly fever, malaria, diarrheal disease, viral hepatitis and cutaneous leishmaniasis. To monitor for these infections, the U.S. military established a state-of-the-art diagnostic laboratory in Saudi Arabia, which was involved in the collection of extensive surveillance data during Operations Desert Shield and Desert Storm.

In the earliest stages of deployment, when the weather was extremely hot, outbreaks of common traveler's diarrhea were frequent. However, there were no laboratory-confirmed cases of more severe cholera, typhoid fever, amoebic dysentery or giardiasis. Acute vomiting due to viral gastroenteritis became a problem after the weather became cooler in late 1990. Acute upper respiratory illnesses also were frequent during periods of crowding.

Rare Problem

Despite active surveillance, there was no documented case of sandfly fever or outbreaks of illness consistent with insect-transmitted infections during the war. There was one confirmed case of West Nile fever (an endemic infection in this region), seven cases of malaria among U.S. troops who went into southern Iraq, three possible cases of Q fever and one death due to meningococcal meningitis. Brucellosis was not diagnosed among U.S. troops, and viral hepatitis was a rare problem.

A combination of factors was probably responsible for very low rates of serious infectious diseases during the Gulf War deployment. For one, rapid medical care and effective treatment were available for infectious diseases. In addition, extensive preventive medicine efforts — vaccinations, immune globulin for hepatitis A prevention, use of insecticides and repellents, camp sanitation measures and inspection of food and water supplies — reduced the risk of infectious diseases. Lastly, limited contact with local populations lowered infectious disease transmission.

Two unplanned factors also may have played a major role in preventing infectious disease problems: the time of the year when most troops were deployed (the cooler winter months) and the location of deployment (the barren desert). Cold weather reduced insect activity at the height of the buildup in January 1991, and the risk of disease transmission was lowered by deploying most troops away from oases and rivers where insects and animals that host infectious diseases are more abundant.



Leishmaniasis

Since the Gulf War, one chronic infectious disease — viscerotropic leishmaniasis — definitely has been linked to service in the Persian Gulf. This sandfly-transmitted infection has been diagnosed in just 12 U.S. veterans and none of the other coalition troops.

Viscerotropic leishmaniasis is a milder form of systemic leishmanial infection caused by a one-celled parasite, *Leishmania tropica*. *L. tropica* infection is not thought to be a widespread cause of chronic symptoms among veterans, because there have been no further cases in eight years and because all but one infected veteran had objective signs of disease that would be apparent on physical examination, principally due to an elevated temperature and an enlarged liver or spleen.

Prior to the deployment of massive numbers of U.S. troops to this region of the world, viscerotropic leishmaniasis had not been identified in local inhabitants or in the large population of foreign guest workers. However, cutaneous leishmaniasis is a relatively frequent problem in this region. This infection of the skin, which causes a characteristic skin rash, has been diagnosed in 20 U.S. Gulf War veterans.

None of the other endemic infectious diseases that troops encountered during this wartime deployment are likely causes of chronic health problems. Additionally, in over 100,000 clinical registry examinations and an epidemiological study conducted by the CDC, no indication was found of an infectious etiology for chronic symptoms. Moreover, a characteristic sign of an infectious process or immune dysfunction has not been identified in registry examinations, including a unique skin rash, lymphadenopathy, hepatosplenomegaly, transaminase elevations or hematological abnormalities. Probably all of these abnormalities are found in some veterans in the Registry.

Other Hypotheses

However, in addition to chronic leishmaniasis, two hypotheses that chronic bacterial infections are the cause of long-term health problems among Gulf War veterans have elicited interest among veterans. One hypothesis involves possible infection with the *Mycoplasma* bacterium, either as a natural infection (possibly facilitated by crowding during deployment) or as a genetically engineered biological warfare (BW) agent. This hypothesis was developed by a well-known cancer researcher whose stepdaughter developed an unexplained illness after returning from the Gulf War. Subsequently, similar illnesses developed in other family members and household pets. There also have been reports by individual veterans that their chronic symptoms improve with tetracycline and doxycycline antibiotic therapy. In one published study, however, no association was found between *Mycoplasma fermentans* infection and either deployment to the Persian Gulf or postwar symptoms.



The other hypothesis involves the possibility of a chronic bacterial coccal infection. This postulated systemic infection cannot be cultured in blood samples but can be identified by observing gram positive cocci and shells of dead cocci, “exploded” in specially evaluated samples of urine sediment. This hypothesis originated from pre-Gulf War observations of a clinician who noted that patients with chronic, unexplained illnesses, like chronic fatigue syndrome, seemed to respond to antibiotic therapy. Interestingly, this same hypothesis was first proposed in 1915 to explain chronic health problems among military personnel.

These two hypotheses of a chronic bacterial infection are being investigated in separate antibiotic treatment trials. In one study that will cost 12 million dollars, a double-blind treatment trial has been instituted by the VA as a Multi-site Cooperative Study at 30 VA and DoD clinical centers. Either doxycycline or placebo will be given over a one-year period to approximately 450 veterans who are positive for *Mycoplasma* genetic material by polymerase chain reaction. Study subjects will be followed for changes in functional status and symptoms, including fatigue and neurocognitive problems. In the other treatment trial, which received three million dollars in funding from the U.S. Congress, various antibiotics are being administered to Gulf War veterans with unexplained symptoms.

If a favorable response is found in either of these treatment trials, further study will be necessary before antibiotic therapy can be recommended for the treatment of Gulf War veterans. First, the results will have to be independently verified. Second, the mechanism of action of antibiotic therapy will have to be determined; that is, whether the response is due to the elimination of a specific infectious agent or whether the effect is due to some other action of drug therapy. Finally, further research will be necessary to determine the most effective treatment regimen.

A final infectious disease hypothesis put forward to explain chronic health problems among Gulf War veterans involves possible exposure to BW agents. However, there was no apparent use of biological agents in the Gulf War. A biologic agent was never isolated during the conflict. Most BW agents are designed to be deadly in minute quantities, but there was no cluster of combat casualties consistent with exposure to highly lethal biological weapons, such as anthrax spores or botulinum toxin.

Conclusion

In conclusion, clinical and epidemiological studies consistently have proven that Gulf War veterans are experiencing a wide range of health problems. Infectious diseases, however, have not been shown to be a major cause of chronic illnesses. After 10 years of intense clinical observation and study, it is increasingly unlikely that an infectious or immune process could cause serious health problems and remain undetected.



Although infectious diseases have not been a major problem, occult leishmanial infection could become manifest over time among a few Gulf War veterans. Leishmaniasis should, therefore, be considered when clinically indicated by objective signs of infection. Diagnosis may require repeated biopsies of bone marrow or lymph nodes to identify the parasite, because currently there is no accurate skin or blood test. Treatment for visceral leishmaniasis can be toxic and is not recommended unless the infection is causing chronic health problems.

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CHAPTER 5 DISABILITY COMPENSATION AND UNDIAGNOSED ILLNESSES

Gulf War veterans, like other veterans, who are disabled by injury or disease incurred or aggravated during active service in the line of duty during wartime or peacetime service, and discharged or separated under other than dishonorable conditions, are eligible for monthly payments from the Department of Veterans Affairs (VA).

The amount of these payments, called disability compensation, is based on the degree of disability. Disability is rated from 0 percent to 100 percent in increments of 10 percent disability. For the year 2001, monthly payment rates range from \$101 for a 10 percent rating to \$2,107 for 100 percent.

Requirements

Generally, in a claim for these service-connected benefits, VA requires: (1) satisfactory medical evidence of a current disability; (2) satisfactory evidence that a disease or injury was incurred in or aggravated by military service; and (3) satisfactory medical evidence that the in-service incurrence or aggravation caused or contributed to the current disability. Gulf War veterans may qualify for disability compensation under these rules or under special rules, described below, established for Gulf War veterans with undiagnosed illnesses.

Additional amounts are paid to certain veterans with severe disabilities and certain veterans with dependents. VA has several pamphlets describing VA benefits. They are available at www.va.gov/publ/direc/eds/edspamph.htm.

Mere exposure to various agents, environmental hazards, or medicines in the Gulf War does not automatically qualify Gulf War veterans for compensation. As mentioned above, payments are based on disabilities, and those disabilities must be associated with military service. Many Gulf War veterans who were exposed to a wide range of potentially dangerous substances during their military service do not have a disabling condition. Some Gulf War veterans have disabilities clearly unrelated to their military service.

Legislation was enacted in 1998, the “Veterans’ Programs Enhancement Act of 1998,” Public Law 105-368, that requires VA to contract with the National Academy of Sciences (NAS) for a series of comprehensive reviews and assessments of available information to determine whether there is an association between illnesses experienced by Gulf War veterans exposed to one or more agents, hazards or medicines during the Gulf War. The NAS reports its findings and recommendations to the Secretary of Veterans Affairs, who is required to evaluate these reports and provide recommendations to Congress as to whether such scientific evidence would warrant a presumption of service connection. The initial IOM report was



published in September 2000.

Under the law, disability compensation can only be approved for conditions incurred in or aggravated during military service. When the illness was present during service, the connection may be clear. When there is a latency period between onset of illness, the connection may be more controversial.

Undiagnosed Illnesses

Under Public Law 103-466, the “Veterans’ Benefits Improvement Act of 1994,” VA also provides compensation benefits to Gulf War veterans who are chronically disabled by undiagnosed illnesses when certain conditions are met. This legislation only authorizes VA to pay compensation for disabilities that cannot be diagnosed as a specific disease or injury. This is a unique benefit for Gulf War veterans.

VA regulations pertaining to undiagnosed illnesses in Gulf War veterans specifies that to be eligible for such compensation, the veteran must have “objective indications of chronic disability” manifested by one or more signs or symptoms, provided that such disability: (1) became manifest either during active military, naval, or air space in the Southwest Asia theater of operations during the Gulf War, or to a degree of 10 percent or more not later than December 31, 2001; and (2) by history, physical examination and laboratory tests cannot be attributed to any known clinical diagnosis.

“Objective indications of chronic disability” refers to “both signs in the medical sense of objective evidence perceptible to an examining physician and other non-medical indicators that are capable of independent verification.”

Signs and symptoms include, but are not limited to: (1) fatigue; (2) skin signs or symptoms, including hair loss; (3) headache; (4) muscle pain; (5) joint pain; (6) neurologic signs or symptoms; (7) neuropsychological signs and symptoms, including memory loss; (8) signs or symptoms involving the respiratory system (upper or lower); (9) sleep disturbances; (10) gastrointestinal signs or symptoms; (11) cardiovascular signs and symptoms; (12) abnormal weight loss; and (13) menstrual disorders.

Disabilities are chronic if they (1) have existed for at least six months, or (2) have exhibited intermittent episodes of improvement and worsening over a six-month period. The six-month period is measured from the earliest date the signs and symptoms manifested.

Compensation cannot be granted under these special rules if there is affirmative evidence (1) that the undiagnosed illness was not incurred during service in the Gulf War; (2) that it was caused by a supervening condition or event after the veteran served in the Gulf region;



or (3) that it is the result of willful misconduct or the abuse of alcohol or drugs by the veteran.

In a claim by a Gulf War veteran for service-connected benefits for an undiagnosed illness, VA requires submission of evidence of (1) active military, naval, or air service in the Southwest Asia theater of operations during the Gulf War; (2) manifestations of one or more signs and symptoms of undiagnosed illness; (3) objective indications of a chronic disability to a degree of 10 percent or more within the specified period; and (4) a nexus between the chronic disability and the undiagnosed illness.

An unintended consequence with this legislation is that two Gulf War veterans with virtually identical symptoms may experience quite different outcomes with their claims for service-connected compensation. Thus, one Gulf War veteran presenting with difficult-to-diagnose symptoms could be diagnosed with chronic fatigue syndrome, which cannot be service-connected under this law because it is a diagnosis. On the other hand, a second veteran with identical symptoms could receive a diagnosis of undiagnosed illness, which is compensable under this law. Clearly, VA physicians should be aware of this distinction and of the consequence this has on a veteran's compensation claim, since under this law, a diagnosis effectively precludes the claimant from establishing service connection for an undiagnosed illness. An improper diagnosis can have unintended but nevertheless disastrous consequences for a veteran's disability claim.

For additional information regarding disability compensation for Gulf War veterans experiencing undiagnosed illness, see Title 38, United States Code, Section 1117, and Title 38, Code of Federal Regulations, Section 3.317.

Survivors' Benefits

Survivors of veterans who died as the result of a service-connected disability may be eligible for monthly Dependency and Indemnity Compensation (DIC) benefits. These survivors (including spouses, children and dependent parents) also may be eligible for education, home loan and medical care benefits.

To Apply

To apply for benefits, veterans and their dependents are encouraged to contact the nearest VA Regional Office. The toll-free number is **1-800-827-1000**.





CHAPTER 6 OUTREACH AND EDUCATION

Outreach is a very important aspect of the Department of Veterans Affairs' program to help Gulf War veterans and their families who are concerned about the possible long-term health consequences of military service in the Gulf War.

Gulf War Veterans Helpline — 1-800-PGW-VETS (1-800-749-8387)

This toll-free telephone service, located at the Gulf War Information Center in the VA Regional Office, St. Louis, MO, provides Gulf War veterans and their families with the latest information on the issues that directly concern them. The helpline offers a series of special, pre-recorded messages covering a wide range of topics 24 hours a day, seven days a week. Gulf War helpline operators are available weekdays to discuss specific situations and to make referrals, primarily to the nearest VA medical center or regional office of jurisdiction. The helpline was established on February 2, 1995, in accordance with Public Law 103-446. About 500,000 calls have been received.

Gulf War Review (originally known as the Persian Gulf Review)

This newsletter is prepared by VA's Environmental Agents Service. The "Review" is published three-to-four times annually to provide information regarding the concerns of Gulf War veterans, their families and others interested in possible, long-term health consequences of military service in the Gulf War. The newsletter provides updated information about Federal government studies and activities related to Gulf War veterans' illnesses. The newsletter is sent to more than 250,000 Gulf War veterans at their homes. More than 400,000 copies are printed. Anyone interested in getting a copy of the "Review" should contact the Gulf War Registry Coordinator at the nearest VA medical center or the Environmental Agents Service (131), Department of Veterans Affairs, 810 Vermont Avenue, N.W., Washington, DC 20420. Twenty-eight issues have been published through July 2001. The newsletters also are on the VA Gulf War website at www.va.gov/gulfwar.

Gulf War Veterans' Illnesses: Questions & Answers

This VA brochure provides answers to 18 commonly asked questions about the health consequences of military service in the Gulf War. Questions include, "Is there a Persian Gulf Syndrome or Gulf War Syndrome?" "What symptoms are Gulf War veterans reporting?" "What is VA doing to help veterans of Desert Shield and Desert Storm?" "Can the spouses and children of Gulf War veterans get free medical examinations?" This publication is



identified as IB 10-41, P94857. It was updated most recently in May 2001. The brochure is also on the VA Gulf War website mentioned above.

A Report to Veterans, Department of Veterans Affairs, Gulf War Research

This two-page VA fact sheet briefly describes the Federal government's commitment and activities regarding Gulf War and related research efforts. This publication explains the mission and efforts of the VA Environmental Hazards Research Centers, the VA large-scale epidemiology studies, new VA research efforts, the role of the National Academy of Sciences' Institute of Medicine, and major research findings. The report is identified as IB 10-42. It was updated as a four-page fact sheet most recently in May 2001. The fact sheet also is on the VA Gulf War website at www.va.gov/gulfwar.

Outreach to Hispanic Gulf War Veterans

VA recognizes that for many veterans and their families, English is not their first language. The largest number of these veterans is Hispanics. To enhance outreach efforts to the Hispanic community, the Questions & Answers brochure and research fact sheet described above have been translated into Spanish. The Questions & Answers brochure in Spanish is identified as IB 10-41, P94873/ Marzo 2000. The Research report is identified as IB 10-42, P95242, Marzo 2000. These Spanish language publications are being updated.

Gulf War Posters

In April 1992, VA produced and widely disseminated a poster which encouraged Gulf War veterans to contact the nearest VA medical center for information and assistance concerning VA's Gulf War Registry Medical Examination Program. In April 1998, a revised poster was produced with the message "VA Cares About Gulf War Veterans." The posters were produced in two sizes. They measure 11" x 14" and 17" x 22". The most recent poster is identified as VA Poster 10-83 (Revised), April 1998.

Gulf War Exhibits

In 1993, VA created two exhibits designed to heighten awareness of the Department's response to the varied concerns of Gulf War veterans. In April 1998, VA replaced these exhibits with new, more up-to-date exhibits. The 1998 "VA Cares About Gulf War Veterans" exhibits are designed to more effectively communicate information about VA programs to respond to the problems and concerns of Gulf War veterans and their families regarding the possible, long-term health consequences of military service in Operations



Desert Shield and Desert Storm. These exhibits highlight the major components of VA's program (that is, medical care, disability compensation, outreach and education and scientific research). As with the earlier version, VA medical centers throughout the nation have borrowed these exhibits for health fairs and other gatherings. The 1998 exhibits were produced in two sizes, a room-sized version that stands 7'6" and a three-foot table top exhibit. Five copies of the table top exhibit were built. The large exhibit is identified as E-98-1759; the table top is E-98-1760. VA medical centers requesting to borrow either of the exhibits should submit VA-Form 3-2757, Request for Exhibit Presentation, to the Environmental Agents Service (131) in VA Central Office. That office plans to decentralize these table top exhibits in the near future.

“Town Hall” Meetings

VA officials have actively participated in numerous meetings throughout the nation to share information with Gulf War veterans and their families about VA program initiatives. These meetings are designed to promote direct communication between VA officials (including researchers, policy-makers and key administrative personnel) and the people they serve. VA sponsored several of these meetings and has participated in many meetings organized by the Office of the Special Assistant for Gulf War Illnesses, a Department of Defense unit.

Persian Gulf Family Support Program

Shortly following the Gulf War, VA established the Persian Gulf Family Support Program (PGFSP) that worked with the Veterans' Benefits Administration, veterans' service organizations, the American Red Cross, vet centers, and the National Guard and Reserve Units to assure that Gulf War veterans are aware of the full range of services available to them. Thousands of Gulf War veterans and their families received counseling through this program. The PGFSP was one of the first VA programs in which family members were provided services, whether or not the veterans was actively involved. The outreach efforts initiated by PGFSP varied widely by station. Social Work Service oversaw this program. The program, authorized by Section 121, Public Law 102-405, was not renewed when it expired in September 1994.

Fact Sheets and National News Releases

The VA Office of Public Affairs maintains current fact sheets on Gulf War issues and periodically produces national news releases, providing updated information about pertinent research, legislation and benefit changes.





VA Field Staff

Each VA medical center has a Gulf War Registry Physician and a Gulf War Registry Coordinator. Registry Physicians are responsible for the clinical management of the Gulf War program at the VA facility where they work. These doctors meet with concerned veterans, conduct medical examinations, document medical problems and answer health-related questions from Gulf War veterans and their families. Gulf War Registry Coordinators handle Gulf War Registry program administrative matters at VA health care facilities. They schedule appointments, review records for accuracy and completeness and collect data for reporting purposes.

VA-ONLINE 1-800-US1-VETS (1-800-871-8387)

VA provides information on benefits, medical care and research initiatives on an electronic bulletin board available 24 hours a day. It can be accessed by callers with a personal computer that includes a modem and a communications package. The toll-free number is listed above.

Special Mailings

These mailings are sent to participants in the Gulf Registry when needed. Several years ago, the Secretary of Veterans Affairs sent letters informing veterans that VA will review disability compensation claims previously filed by veterans who believe they were exposed to environmental hazards while serving in the theater of operations. The letter also encouraged veterans who have not filed claims to do so if they think they may be entitled to benefits.

Briefings for Separating Service Members and Others

VA conducts numerous briefings with active duty service personnel, Reservists and National Guard members. Information about the helpline and medical services and benefits available to Gulf War veterans are described in these briefings, including those conducted in support of the Transition Assistance Program, which VA jointly sponsors with the Departments of Defense and Labor to assist separating service members in making a smooth transition to civilian life.



VA Public Service Announcements (PSAs)

VA has broadcast PSAs over public and private stations to publicize the helpline and other aspects of VA's program on behalf of Gulf War veterans. The Gulf War spots are in very limited supply and may soon be outdated. VA will produce additional Gulf War-related PSAs, if warranted by events.

Veterans Services Representatives (VSR)

Veterans Services Representatives (VSR), located in VA regional offices and many medical centers, possess a wealth of information about the wide range of VA benefits. These representatives have all the forms necessary to apply for VA benefits, including disability compensation, and dependency and indemnity compensation. VSR's also assist veterans and their survivors in completing these forms, if necessary.

VA Vet Center

VA Vet Center personnel also are very helpful to Gulf War veterans experiencing difficulties readjusting to civilian life. There are more than 200 vet centers nationwide. Vet centers offer individual, group and family counseling.

VA National Headquarters

The Environmental Agents Service in Washington, DC, is an excellent source of information about Gulf War veterans' illnesses. The office was organized more than 20 years ago, and has been responding to Gulf War veterans' concerns since they first were raised. While the staff is quite small, many veterans have found the personnel to be very helpful. Comments, suggestions and criticisms about VA's Gulf War veterans' program always are welcome. The mailing address is Environmental Agents Service (131), VA Central Office, 810 Vermont Avenue, N.W., Washington, DC 20420. The telephone number is 1-202-273-8580.

Annual Report to Congress — Federally Sponsored Research on Gulf War Veterans' Illnesses

In 1993, President Clinton designated the Secretary of Veterans Affairs to coordinate research into the health consequences of service in the Gulf War. As part of this coordination role, VA is required to submit a yearly report to Congress on the results and progress of research activities by the Executive Branch of the Federal Government. This report is prepared by the Research Working Group of the Military and Veterans Health Coordinating Board (previously known as the Persian Gulf Veterans Coordinating Board). The Board is co-chaired by the Secretaries of Defense, Health and Human Services and Veterans Affairs.



Federal Benefits for Veterans and Dependents

This booklet, which is updated annually by VA, includes sections on benefits and services for Gulf War veterans who may have been adversely affected by toxic exposures in the Gulf War. The booklet is among the most popular sold by the U.S. Government Printing Office. It also is available in Spanish.

A great deal of information is available on the VA Gulf War veterans' website at www.va.gov/gulfwar.

Department of Defense (DoD) Outreach Efforts

The DoD has taken a number of concrete measures to reach out to Gulf War participants who may be ill due to their military service in Southwest Asia. On June 23, 1994, the DoD established their **Gulf War Medical Registry Hotline** — **1-800-796-9699** to refer eligible persons to medical facilities to participate in DoD's Comprehensive Clinical Evaluation Program. DoD later established a second toll-free hotline number — **1-800-472-6261** — for reporting of first-hand information about “**incidents**” that occurred in the Southwest Asia theater of operations during the Gulf War that may be related to health problems experienced by military personnel who served in the war. DoD has an excellent website for Gulf War issues at <http://www.gulflink.osd.mil>.

Other Non-VA Sources

Veterans service organizations (such as The American Legion, Veterans of Foreign Wars of the United States, Disabled American Veterans and numerous other veterans' groups) and State government entities (such as Departments or Divisions of Veterans Affairs and Departments of Health) also have assisted many veterans.

Congressional committees have held many hearings on Gulf War veterans' illnesses. The Senate and House Committees on Veterans' Affairs and the House Reform and Oversight Subcommittee on Human Resources and Intergovernmental Relations have been particularly interested in this subject. VA representatives often provide testimony at these hearings.