

The Persian Gulf Experience and Health

National Institutes of Health
Technology Assessment Workshop Statement
April 27–29, 1994

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Reference Information

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Introduction

Following the return of U.S. and coalition forces from the complex environment of the Persian Gulf region during Operations Desert Shield and Desert Storm and the operational conditions of the military deployment, a variety of health effects have been reported. Many troops were exposed to potentially adverse substances and experiences present in this wartime environment—fumes and smoke from military operations, oil well fires, diesel exhaust, toxic paints, pesticides, sand, depleted uranium, infectious agents, chemoprophylactic agents, and multiple immunizations; some troops are convinced they were exposed to chemical or biological weapons. Few combat casualties occurred, but substantial transient gastrointestinal and respiratory symptoms were seen during the troop buildup and immediately after the short conflict. Since then, there have been increasing reports of illness from troops who were participants in these operations, and many attribute their health problems to these experiences. Many of the cases include combinations of nonspecific symptoms of fatigue, skin rash, muscle and joint pain, headache, loss of memory, shortness of breath, and gastrointestinal and respiratory symptoms, which may not fit readily into a common diagnosis. In the absence of clear and complete diagnosis and effective treatment of all symptoms, the concept of a distinct syndrome that is peculiar to the Gulf War theater of operations has been suggested. Some veterans have reported illnesses in their spouses and birth defects in children conceived after the conflict and are concerned about the spread of disease as a public health issue.

A number of governmental responses have been initiated as a result of the Gulf War veterans' complaints. The Department of Defense and the Department of Veterans Affairs have begun registration of Persian Gulf veterans. Special referral centers for clinical evaluation of complaints have been established by the Department of Veterans Affairs, and research proposals have been solicited to better understand their cause, diagnosis, and treatment.

The intent of this Technology Assessment Workshop was to examine the information provided to the panel on these reports of illness, to assess the types and extent of environmental exposures of troops serving in the Persian Gulf, to determine the adequacy of information on the prevalence and incidence of unusual illnesses, and to attempt to develop working case definitions for those illnesses. In addition, plausible etiologies and biological explanations for the illnesses were considered, and recommendations for future research were made.

After 1½ days of medical, scientific, and Government presentations by academic and Federal investigators, testimony of Gulf War veterans, and questioning and discussion by a public audience, this independent, non-Federal panel weighed the objective and subjective evidence and wrote a statement in response to the following key questions:

1. What is the evidence for an increased incidence of unexpected illnesses attributable to service in the Persian Gulf War?
2. If unexpected illnesses have occurred, what are the components of the most practical working case definition(s) based on the existing data?
3. If unexpected illnesses have occurred, what are the plausible etiologies and biological explanations for these unexpected illnesses?
4. What future research is necessary?

This workshop was sponsored by the NIH Office of Medical Applications of Research, the U.S. Department of Health and Human Services, the U.S. Department of Defense, the U.S. Department of Veterans Affairs, and the U.S. Environmental Protection Agency.

Question 1: *What is the evidence for an increased incidence of unexpected illnesses attributable to service in the Persian Gulf War?*

Definition of Unexpected Illness

Under conditions of the Persian Gulf War, certain infectious diseases, such as acute viral, bacterial, and parasitic respiratory and gastrointestinal infections due to crowded living conditions, as well as endemic infectious diseases such as leishmaniasis, schistosomiasis, and malaria, were expected. Noninfectious respiratory conditions including reactive airways diseases, interstitial lung diseases, and diminished lung function were not expected but are explainable and diagnosable. Other expected conditions include post-traumatic stress disorders and various skin disorders such as hypersensitivity dermatitis and chemical dermatitis. **In this report, unexpected illnesses are defined as previously unrecognized and unanticipated symptom complexes or illnesses that do not fit traditional diagnostic categories.**

An Assessment of the Incidence of the Unexpected Illnesses

The available data are too limited to draw any conclusions regarding the incidence of unexpected illnesses in this population. In general, all the data presented are numbers of individuals reporting symptoms, and those studied to date may not be representative of all individuals at risk for developing these symptoms. Since all Gulf War veterans or a representative sample of these veterans has not been surveyed for presence of symptoms, it is not possible to calculate the incidence of unexpected illnesses. In addition, we do not have comprehensive information on the dates of onset of illness. Such information is needed to estimate incidence and trends over time in the occurrence of illness.

Nevertheless, the data that were provided to the panel suggest that deployed active-duty personnel and deployed reservists reported more symptoms than did their nondeployed counterparts and that veterans of the Gulf War reported more illnesses than did veterans of previous wars. Data on the symptom profile reported in the Gulf War Registry were also compared with those reported for Vietnam veterans in the Agent Orange Registry. Fatigue, muscle and joint pain, headache, and shortness of breath were more frequent among those who served in the

Persian Gulf area; skin rash was less frequent. Since data were not collected in a comparable fashion for the two registries, only limited conclusions can be drawn from this study.

In the case of leishmaniasis, a novel and unexpected manifestation of the disease was identified—viscerotropic leishmaniasis. Because this disease is difficult to diagnose, its true incidence is unknown. The cases reported are minimum estimates of the true number of infected people.

Although congenital malformations have been reported in the offspring of people who served in the Persian Gulf area, the currently available data are not sufficient to determine whether the incidence is increased and thus may be unexpected.

Question 2: *If unexpected illnesses have occurred, what are the components of the most practical working case definition(s) based on the existing data?*

It appears from the information presented that some Persian Gulf veterans have symptoms that are not readily explained by using established disease categories. Under these circumstances, it would be helpful to establish a single case definition to assist in evaluating and managing these veterans. However, a single case definition may not be sufficient, since there may be more than one disease category. Therefore, an evolving case definition might be more appropriately used in developing a research strategy.

In order to describe better the particular symptom complex needed for a case definition or definitions, other cohorts of veterans should be evaluated and compared with the Persian Gulf veterans. These cohorts would consist of veterans who were deployed to other foreign locations for combat and noncombat situations and/or veterans who were not deployed. Information should be obtained from these veterans using standardized and symptom-specific evaluations. These evaluations could be conducted in conveniently accessible regional centers, with monitoring and analysis of data at a single location. In addition, evaluation of Persian Gulf veterans should be continued at these same locations using identical standardized protocols. Case definitions could then be developed by means of these comparisons.

For the above reasons, it is impossible at this time to establish a single case definition. Furthermore, a premature attempt to establish a case definition for this illness may be misleading and inaccurate. **Eligibility for medical care need not depend on case definition.**

Question 3: *If unexpected illnesses have occurred, what are the plausible etiologies and biological explanations for these unexpected illnesses?*

The Persian Gulf War was an experience of unprecedented stress for our military and their families. Reserve and National Guard units were rapidly mobilized to join 500,000 active-duty troops in southwest Asia. The military command anticipated that chemical and/or biological weapons would be used. Detectors signaled the presence of chemical weapons on several occasions that caused increased anxiety. As many as 50,000 casualties were expected in a full-scale 15-day war with Iraq. Tactical strategy demanded secrecy. Troops could not be informed about the timing and objectives of their actual assignments. Public knowledge that Iraq had stockpiles and capabilities of delivering chemical and biological weapons contributed to mass anxiety.

The complex set of exposures and stressors made the Persian Gulf tour unique. Individuals who were deployed had severe psychological stresses upon entering the area. All had multiple vaccines and medications administered during this period, worked long hours, and lived in crowded and often unsanitary conditions among flies, snakes, spiders, and scorpions. The chemical contaminants from oil fires, burning dumps (feces and trash), fuels, and solvents were ubiquitous. The climate exhibited temperature extremes in a sand/dust environment. The threat of biological and chemical warfare was omnipresent. **In this report, no single or multiple etiology or biological explanation for the reported symptoms was identified from the data available to the panel.** In this setting, standard dose-and-effect relationships may be altered. Possible causative or contributing factors to the unexplained symptoms are reviewed below.

Leishmaniasis

Thirty-one proven cases of leishmaniasis were diagnosed by parasite identification. These cases probably represent a small subset of the expected population of infected persons. Visceral leishmaniasis can present with typical manifestations (hepatosplenomegaly, fever, weight loss, pancytopenia) and/or vague, nonspecific symptoms (fatigue, low-grade fever, gastrointestinal symptoms); or it may be subclinical. The finding of visceral involvement by *Leishmania tropica* in one

report is novel; it would constitute a new disease entity that could be missed by conventional diagnostic procedures. The natural history of this so-called viscerotropic leishmaniasis is unknown.

Many of the proven cases of leishmaniasis had nonspecific symptoms, including chronic fatigue, gastrointestinal symptoms, and low-grade fever—symptoms shared by Persian Gulf veterans with unexplained symptoms. The delayed onset and prolonged duration of leishmaniasis are also compatible with the symptom patterns of some Gulf War veterans. Certainly, **some** of the illnesses of the veterans could be attributable to this form of leishmaniasis.

The standard diagnostic tests (bone marrow, skin tests, serology) may not be sensitive enough to detect infection in this disease, and therefore, other methods need to be applied. These methods should be made available as rapidly as possible and include (1) T cell proliferation assay in response to *L. tropica* antigens, (2) cytokine profile analysis, and (3) detection of *L. tropica* DNA in bone marrow based on polymerase chain reaction (PCR). The underlying prevalence is likely to be substantially higher than reported and, thus, should be part of the primary Veterans Affairs (VA) diagnostic protocol(s).

Petroleum

Exposure to petroleum vapors, solvents, and combustion products was common during the Persian Gulf War. Inhalation was evidently the dominant route of exposure, but ingestion and dermal exposures were important in some circumstances. Petroleum (kerosene, diesel fuels, and leaded gasoline) was used for heating. Petroleum products including diesel fuels were used as sand/dust suppressants. Mobile armament and vehicles used diesel and gasoline fuels. Oil well fires resulted in exposures to carbonaceous particulates composed of metals, as well as unburned and partially pyrolyzed hydrocarbons. Oil on surfaces was partially volatilized, resulting in the distillation of lighter weight hydrocarbons. Where crude oil was burned or deposited, inorganic gases (SO₂, NO₂, CO, CO₂, H₂S, reduced sulfur compounds) were released. Engine exhaust, burning, and evaporating petroleum would also result in increased exposures to aromatics, aliphatic and aldehyde gaseous compounds, and a great number of semivolatile organic compounds.

Exposures to petroleum-related pollutants occurred throughout the Persian Gulf. For many military personnel, both chronic and acute exposures to respiratory irritants, carcinogens, and neurotoxic compounds were highest during winter-time encampments in Saudi Arabia. Beginning in late February, military personnel in Kuwait and eastern Saudi Arabia were exposed to gases and particulate soot from the oil well fires. Exposures were more frequent and severe for those in closer proximity to the sabotaged wells.

The practices of spreading oily dust suppressants, burning trash and human waste, and using gasoline and diesel fuels for unvented heaters are documented. There were no reported measurements of ambient or indoor pollutants. On the basis of published reports on residential kerosene heater studies, elevated concentrations of SO₂, NO₂, HNO₂, H₂SO₄, NH₄HSO₄, CO, lead, respirable particulates, and other pollutants would be expected. Elevated concentrations lasting throughout the winter nights would have been repeated occurrences in tents where nonissued fuels were used. Exposures could have exceeded Federal standards and World Health Organization (WHO) health guidelines. Elevated blood lead levels, increased airway resistance, and persistent wheezing and coughing, as well as respiratory infections, might be expected. Repeated and chronic exposures to these combustion pollutants could result in permanent impairment.

Open burning of fuels, with the exception of the oil wells, would have produced localized plumes. Diesel exhaust from electric generators could be reentrained into ventilation systems. The spreading of fuels for dust suppression as well as refueling operations would certainly have resulted in petroleum vapor exposures. Transient levels of benzene, toluene, ethylbenzene, and xylene exceeding 1 ppm could have occurred. Prolonged exposures to these vapor compounds may result in symptoms of lightheadedness, mucosal irritation, fatigue, and cognitive dysfunction. Since benzene and some polycyclic aromatic hydrocarbons are known human carcinogens, some exposures might increase long-term cancer risk.

Oil well fires produced dense clouds of soot, liquid aerosols, and gases. Particulate concentrations between 500 and 2,000 µg/m³ would have occurred during fumigation. Hydrogen sulfide, sulfur dioxide, and

reduced sulfur compounds, together with the organic carbon and metals in the particulate phase, would cause pulmonary irritations. It is possible that prolonged exposure might lead to sinusitis, bronchiolitis, pneumonitis, asthma, or chronic obstructive pulmonary disease. Comprehensive air monitoring did not start until early May 1991, and it missed the most severe exposures to ground troops in Kuwait.

Sand Dust

Desert sand can be eroded by wind and mechanical disruption by vehicles. Troops experienced a dusty environment where ambient concentrations have been measured as high as a few milligrams per cubic meter. Inhalation of finely ground sand and associated dust certainly could have irritated upper airways of many and could possibly have exacerbated asthma. Long-term effects of inhaling resuspended sand are unknown, but are not likely to be associated with the complex of symptoms reported by Persian Gulf veterans.

Depleted Uranium

Depleted uranium in an aerosolized form, resulting from impacts and burning of the metal, provided a source of exposure for individuals in certain localized areas. The radioactivity associated with these operations was described as mostly below U.S. standards for acceptable exposure. The quantitation of radiation exposures that occurred should be attempted and the information made available so that any diseases arising in the future that may be connected with this exposure can be properly evaluated. Because of the latent period for most cancers, it is too soon to see significant increases.

Uranium, a heavy metal, causes kidney damage and, when inhaled, can accumulate in the lungs, but no pulmonary toxicity has been reported. The symptoms reported among the Persian Gulf veterans do not appear to be related to the heavy metal, uranium.

Pyridostigmine

Pyridostigmine was fielded as “pretreatment” for nerve agent poisoning in anticipation of chemical warfare. All personnel were provided with pyridostigmine bromide at doses of 30 mg in blister packs

of 21 tablets each. The drug was ordered for self-administration by the major commanding officer when attack was thought to be imminent. The drug was self-administered every 8 hours for up to 7 days or until orders were given for discontinuation. Other coalition troops also used the drug. It is likely that a great majority of ground personnel received at least one dose and probably up to the full 21 tablets dispensed. However, there are reports that some personnel received repeated courses of the drug.

Pyridostigmine inhibits acetylcholinesterase. Short-term adverse drug effects were noted in some personnel including nausea, vomiting, genitourinary effects, headache, rhinorrhea, dizziness, tingling of the extremities, abdominal cramping, and dizziness. Reported side effects ranged from 5 to 50 percent in treated troops. These effects resulted in a medical visit in less than 1 percent of the cases. Pyridostigmine is eliminated primarily in the urine and does not enter the brain. It has an average plasma half-life of approximately 3.7 hours. When given at the prescribed dose and dose frequency, significant plasma or tissue accumulation is unlikely. However, numerous reports suggest that more severe acute effects occurred in Persian Gulf personnel.

Generally considered safe, pyridostigmine has been used in clinical medicine for decades in patients with myasthenia gravis, in doses up to 6,000 mg/day for life. No significant long-term adverse effects have been noted in these patients. Significant drug interactions that might heighten acute or chronic toxicity were not documented in the U.S. forces. Exposure to pesticides might enhance acute effects of pyridostigmine, but are unlikely to have chronic effects at these doses.

Pesticides

Pesticides and rodenticides approved by the Environmental Protection Agency were used in vector-borne or rodent disease prevention and control efforts. Application records for these agents do not exist, but their use was unrestricted. Relative quantities of pesticides available for use in operations are available from supply records, but total available tonnage was not available to the panel. Common pesticides used include *d*-phenothrin, chlorpyrifos, resmethrin, malathion, methomyl, lindane, pyrethroids, azamethiphos, and DEET.

Potential acute adverse effects of organophosphates include headache, diarrhea, dizziness, blurred vision, weakness, nausea, cramps, discomfort in the chest, nervousness, sweating, miosis (pinpoint pupils), tearing, salivation, pulmonary edema, uncontrollable muscle twitches, convulsions, coma, and loss of reflexes and sphincter control. Nausea, incoordination, and eye and skin irritation can occur following acute pyrethroid exposure. Polyneuropathy can occur 2 to 3 weeks following high-level exposure to some organophosphates (malathion, chlorpyrifos).

Acute biological responses to pesticides in the Gulf War were not reported. Chronic responses to organophosphates are considered unlikely because of the absence of reported polyneuropathy among the examined veterans.

Chemical Agent Resistant Coatings

Vehicles and equipment were painted with chemical agent resistant coatings (CARCs), either before being shipped to the Persian Gulf or at the port in Dammam/Dhahran. It was reported that CARC painting was conducted by civilian workers and a guard unit from Florida. CARCs contain toluene diisocyanate, which could lead to sensitization of the lung, including asthma. The exposures are considered to be limited to a small number of veterans.

Biological and Chemical Warfare Agents

Exposure to chemical and biological warfare agents remains controversial. Many veterans report that exposures occurred. There were numerous sightings of dead animals. The Czechs reported detection of both sarin and mustard gas in separate incidents. The Department of Defense reported no evidence of exposures. The preliminary report of the Department of Defense's "Defense Science Board," which was specifically charged to evaluate chemical and biological warfare, was not provided to the panel. Until it can be unequivocally established that chemical and/or biological weapons were not used and that troops were not exposed to plumes of destroyed stockpiles, the possibility remains that some symptoms are chronic manifestations of such exposure.

Vaccines

The Persian Gulf War participants were vaccinated against expected infectious diseases, as well as against two agents of biological warfare—anthrax and botulinum toxin. All the vaccines, except for the latter two, are standard reagents administered to all enlisted personnel and are also routinely given to civilians. The anthrax and botulinum vaccines, which are produced by the Michigan State Public Health Department, have been available for many years and have been given to thousands of civilian and military personnel. No long-term adverse effects have been documented.

Stressors

The stresses of the Persian Gulf experience have been of such a nature that the form of symptoms reported as a post-traumatic stress disorder (PTSD) needs to be understood in light of the unique types of stresses presented by that experience. The stresses include sudden mobilization for military service in a hot, sandy, strange southwest Asian desert; exposure to the largest, most dramatic oil well fires in history, which spilled smoke and oil over a vast area; and potential chemical and biological warfare. Although warfare has always been stressful and fear-inducing, the Persian Gulf War was the first combat experience in which the real threat of chemical and biological warfare was known to troops before entering the combat area.

The symptoms reported by veterans of the Persian Gulf War are multisystemic, often unassociated with objective signs of pathology, and not easily distinguished from other multisystem symptom complexes that have been described in the *9th International Classification of Diseases*, such as chronic fatigue, fibromyalgia, and somatiform disorders. A variety of symptoms of unknown etiology has developed in some Persian Gulf veterans, accompanied by what appears to be a post-traumatic stress disorder that is distinct from or overlapping with classic PTSD. Perhaps the clinicians who applied standard criteria for PTSD from: *Third Edition, Revised the Diagnostic and Statistical Manual of Mental Disorders* = (DSM-III-R), such as numbing and flashbacks, may not have documented or paid sufficient attention to high

body concerns and high physical symptom conditions in Persian Gulf veterans that reflect a post-traumatic stress disorder not emphasized by classic PTSD criteria. Some Persian Gulf veterans' behavioral responses, far from being numbed, are active, vivid anxiety manifestations expressed as multisystem physical symptoms. It is possible that the expression of post-traumatic distress may be distinct in the Persian Gulf experience and may take the form of somatic and multisystem symptoms rather than classic PTSD numbness and flashbacks. We are not suggesting that there is no physical basis for the reported symptoms, but that expression of the reported symptoms of post-traumatic stress disorder represents a psychophysiological response that needs to be evaluated.

Question 4: *What future research is necessary?*

- It is important that a more accurate estimate of the symptom prevalence be established. A short health questionnaire could be sent to all 700,000 veterans, or to a representative sample, including dates of service and a symptom checklist including illness in family members.
- A coordinated Department of Veterans Affairs and Department of Defense hospital-based case assessment protocol should be developed to provide a uniformly thorough assessment, diagnosis, and treatment of all Persian Gulf veterans with multisystem illness. An assessment strategy modeled after the Centers for Disease Control and Prevention (CDC) protocol for chronic fatigue syndrome is recommended. Such systematic diagnosis and evaluation would ensure the identification of specific treatable disease, would minimize the likelihood of misdiagnosis and inappropriate treatment, and would lead to a case definition needed for clinical, epidemiological, and other purposes.
- Only by comparing symptom rates among population groups can true underlying differences and unusual illnesses be revealed. Cohort studies are needed in which deployed and nondeployed soldiers are compared. Comparison populations should include those deployed elsewhere. Also needed are well-designed case-control studies that include detailed exposure information for those reporting symptoms and for appropriately selected controls. Case-control studies will permit the evaluation of specific exposures as possible etiologic agents for the illnesses reported by Gulf War veterans. Family studies should be included when appropriate.
- Pulmonary symptomatology is the most common reason for disability applications. Pulmonary functions of combat and support troops can be determined directly. The military should, therefore, conduct a retrospective cohort study to investigate pulmonary function related to oil fire plume exposures.
- The military should simulate the indoor situations associated with unvented heaters and other exposure scenarios involving petroleum, insecticides, and spray paints among others. Physical and mathematical modeling is a reasonable approach to estimating

concentrations in situations representative of those experienced in the Persian Gulf operation. The exposure estimates obtained from these simulations should be used in conjunction with questionnaires to estimate individual exposure in the case-control and cohort studies described above.

- Research is needed to establish the relationship of stressors of deployment and combat to the constellation of symptoms afflicting some Gulf War veterans. The Department of Defense should anticipate how specific features of contemporary deployment and combat may contribute to acute and delayed psychophysiological dysfunction and should develop educational, training, and instructional protocols that reduce deployment and combat stress.
- The Department of Veterans Affairs should develop more responsive and effective approaches to diagnosis and therapy of veterans affected by stress-related or stress-exacerbated illness. Attention should be devoted to multidisciplinary research and clinical approaches that identify treatable conditions, provide objective assessments of physiological and neuropsychological dysfunction, and lead to interventional strategies to limit disability due to stress-related symptoms.
- The panel found that few data are available regarding the troops who served in the Persian Gulf and their exposures during that period of service and that data collection that was carried out was initiated only after a considerable delay. The panel therefore strongly recommends that the Department of Defense develop plans for prompt collection of high-quality, relevant data at any time U.S. forces are deployed in the future. The data collected should include baseline data regarding the predeployment health status of the troops, the environmental characteristics of their surroundings, their exposures during deployment, and their health status both at the end of deployment and subsequently. Plans for such data collection should be developed by a multidisciplinary group including clinicians, occupational physicians, epidemiologists, and industrial hygienists, among others. Input from outside the Department of Defense should be solicited before the plan is finalized, and the

final plan should be reviewed and revised periodically thereafter. From the time this planning effort is initiated, the group or individuals who will be responsible for its successful implementation should be clearly designated.

- A previously unrecognized manifestation of leishmaniasis—viscerotropic leishmaniasis—was identified among some veterans suffering from symptoms compatible with the unexplained illness. Research that would facilitate more sensitive diagnosis, as well as identifying appropriate treatment and management of this disease, should be a high priority. A standard evaluation protocol should be established at all VA hospitals to screen veterans suffering from an unexplained illness for this infection.

Conclusions

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

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