Illness in Gulf War Veterans

Causes and Consequences

In 1990 and 1991, 697 000 men and women of the US armed forces served in the Persian Gulf. During their service these veterans were exposed to a wide array of known and potential hazards to health. These risk factors included extremes of heat and cold, blowing dust, smoke from oil well fires, petroleum fuels and their combustion products, pyridostigmine bromide (administered as pretreatment for potential poison gas exposure), anthrax and botulinum toxoid vaccines, depleted uranium (used in certain artillery shells), infectious diseases, chemical warfare agents, pesticides, and pervasive psychological and physiological stress.[1]

See also pp 215, 223, 231, and 238.

Since returning home, many Persian Gulf War veterans have developed illness. Some have specific diseases that clearly resulted from their military service.[2] For example, 32 veterans have been diagnosed with leishmaniasis, and 7 have developed malaria. Several dozen retain fragments of depleted uranium embedded in their bodies, and others sustained traumatic injuries. But perhaps most notably, many more veterans have returned with an array of symptoms—including fatigue, joint pain, gastrointestinal complaints, memory problems, emotional change, impotence, and insomnia—that defy diagnostic classification.

Epidemiologic studies designed to answer fundamental questions about the prevalence, distribution, and causes of illness among Gulf War veterans have been initiated and will continue for many years. A recently published analysis found a 9% higher death rate in Persian Gulf War veterans as compared with other veterans of the same era.[3] This excess mortality was entirely attributable to "external causes," with a particularly striking excess of deaths from motor vehicle injuries, although no excesses of deaths from suicide, homicide, or specific diseases were observed.[3] A study of hospitalization in military hospitals of 547 000 Gulf War veterans who had remained on active duty in the 2 years following the war found no consistent pattern for excess of any particular diseases.[4] Other analyses of illness in specific groups of veterans who had reported high rates of symptoms have confirmed the existence of fatigue, headache, emotional change, and joint pain in these men and women.[5-7] While carefully done, all of these cluster studies have involved relatively small groups of veterans, and all have 2 basic limitations: the groups under investigation are self-selected and their symptoms are self-reported. Consequently, none of these studies has identified specific diagnoses or specific etiologic factors responsible for the veterans' symptoms. Additional epidemiologic studies that have examined cognitive function in selected groups of Gulf War veterans[8-10] have shown slight decrements in memory and concentration.

The 3 reports in this issue of THE JOURNAL by Haley and colleagues[11-13] as well as the study by Schwartz et al[14] represent further important efforts to classify and categorize symptoms in Gulf War veterans.

The studies by Haley et al were performed in 249 members of a Reserve Naval Mobile Construction Battalion that served in the Gulf. Illness has been common in this group, and cognitive function in some members was evaluated previously at the Birmingham Veterans Center.[10] To examine patterns of illness, Haley et al administered a detailed symptom questionnaire to the veterans, 70% of whom reported having had serious health concerns. Then through factor analysis, the authors identified 6 clusters of self-reported symptoms that they grouped into syndromes, with the most strongly clustered symptoms characterized as impaired cognition, confusion-ataxia, and arthromyoneuropathy.[11] To further explore the nature of those syndromes, the investigators performed detailed neuropsychologic studies in 23 veterans with clinical symptoms and in 20 controls. They found evidence of neuropsychologic impairment in the symptomatic veterans as measured by decrements in test scores and evidence of neurologic dysfunction, as characterized by asymmetry in evoked

From the Department of Community Medicine, Mount Sinai School of Medicine, New York, NY. Dr Landrigan is a member of the Presidential Advisory Committee on Gulf War Veterans' Illnesses. He is a Lieutenant Commander, Medical Corps, US Naval Reserve.

Reprints: Philip J. Landrigan, MD, MSc, Department of Community Medicine, Mount Sinai School of Medicine, 1 Gustave L. Levy Place, New York, NY 10029-6594 (e-mail: plandrigan@smtplink.mssm.edu).

potentials and abnormalities of audiovestibular function.[12] Then, on the basis of structured interviews regarding exposures sustained in the Gulf, Haley et al concluded that some cases of neuropsychologic impairment might have been due to DEET and other pesticides, that some may have been due to exposures to chemical warfare agents, and that some may be linked to pyridostigmine bromide.[13]

The study by Schwartz et al is a population-based survey undertaken among a sample of Gulf War veterans from Iowa.[14] Participants were drawn from all branches of the armed services and represented more than 800 military units. Symptom prevalence rates were examined in Gulf War veterans and in Iowa military personnel of the same era who were deployed elsewhere. Compared with military personnel not deployed to the Persian Gulf, Gulf War veterans were found to have significantly higher prevalences of medical and psychological symptoms including depression, cognitive dysfunction, and fibromyalgia. Among Persian Gulf veterans, these conditions were more common among those reporting exposures to solvents, smoke, pesticides, pyridostigmine, and chemical warfare agents than among those not reporting such exposures.

What Is the Scientific Significance of These Findings?

Most important, these studies confirm previous clinical and epidemiologic investigations[5-7] showing that many Persian Gulf War veterans have a variety of troubling and sometimes disabling symptoms. The data of Haley et al confirm previous reports that symptoms are linked in at least some veterans to neuropsychological impairment.[8-10] Each of the studies asks important etiologic questions.

The study by Schwartz et al is particularly robust. It includes a representative sample of all veterans from Iowa who served in the Persian Gulf. Participation rates were high. Meticulous attention was paid to issues of quality control and study methods. A limitation in the study, which Schwartz et al acknowledge, is that all symptoms as well as all exposures were self-reported and thus are subject to recall bias. A second problem derives from the broad range of military units covered. While this breadth enhances the generalizability of the findings, the lack of concentration on any particular unit precludes detailed examination of hazards that may have affected only certain groups of veterans.

The studies by Haley et al[11-13] are ambitious and sophisticated, but have limitations that substantially weaken the authors' strong conclusions. First, the studies are not population based, but rather are focused on a single battalion of naval construction workers, a group whose exposures and experiences may have been quite different from those of most veterans. This aspect increases the depth of the studies, but limits the generalizability of the findings. Second, only 41% of the battalion participated in the examinations. That relatively low participation rate raises the possibility of selection bias; ie, those who participated may be significantly different in certain important characteristics from those who chose not to join the study—for example, in the prevalence, severity, or patterns of illness. In fact, only 43% of nonparticipants who were surveyed reported serious health problems since the war, compared with 70% of participants who did so. Third, virtually all information on illnesses is self-reported; detailed clinical and neuropsychological examinations were performed on only 23 symptomatic veterans (less than 4% of the battalion), and measurements of motor nerve conduction velocity, the classic test to confirm organophosphate-induced delayed peripheral neuropathy,[15] were made on only 5 veterans. Finally, all exposure data were self-reported. The investigators made no effort to independently or objectively verify exposures.

Haley et al suggest that some cases of illness in members of their population may represent chronic neurotoxicity caused by low-dose exposures to chemical warfare agents. This is an important question that demands serious investigation. The issue of chemical warfare exposure in the Persian Gulf first came to prominence in 1996. At that time the US Department of Defense belatedly acknowledged—after persistent questioning from the Presidential Advisory Committee on Gulf War Veterans' Illnesses—that neurotoxic chemical warfare agents, notably sarin, had been released in certain areas of the Gulf during the destruction after the war of Iraqi ammunition bunkers. A well-documented release occurred during the destruction by US troops of a bunker at Khamisiyah. The veterans examined by Haley et al apparently were not involved in the episode at Khamisiyah.

Acute high-dose exposure to chemical warfare agents, many of which, such as sarin, are based on organophosphate molecules, can cause devastating damage to the nervous system.[16] Survivors of acute sarin poisoning also have been reported to manifest chronic neurotoxity.[17,18] Less is known about the possible chronic consequences of lower-dose, asymptomatic exposures to these agents. The available data argue against the existence of low-dose or delayed neurotoxicity in the absence of acute symptoms, but those data are sparse.[19,20] Further research is needed to determine whether low-dose exposure to chemical warfare agents can cause chronic neurotoxicity. Such research is now under way at the Boston and Portland Veterans Environmental Health Research Centers.

What Is the Message of These Studies for Practicing Physicians?

The data on symptoms confirm what many physicians caring for Gulf War veterans already know, namely, that the illnesses in these men and women are quite real. Whatever their precise etiology, the health problems that Gulf War veterans are experiencing clearly are not the result of malingering or desire for compensation.

The findings on risk factors should instill a sense of etiologic caution in medical practitioners. Clinicians need to recognize that the precise causation of illness in most Persian Gulf War veterans may never be known with certainty. The information on chemical warfare exposure is fascinating, and the delays in release of those data are troubling. However, the link between chemical warfare exposure and disease in Gulf War veterans certainly has not been proven by these studies. Many Gulf War veterans will continue to experience nonspecific symptoms of imprecise etiology. Counseling, support, and symptomatic treatment will continue to be very important. Physicians need to acknowledge that many Gulf War veterans are experiencing stress-related disorders and the physical consequences of stress.[21-23] These conditions should not be hidden or denied, but rather are well-recognized entities that have been studied extensively in survivors of past wars, most notably the Vietnam conflict. As physicians, we should not accept a diagnosis of stress-related disorder in veterans prior to excluding treatable physical factors, but at

the same time, we need to recognize the pervasive presence of stress-related illness such as hypertension, fibromyalgia, and chronic fatigue among Persian Gulf War veterans and manage these illnesses appropriately. As a nation, we need to get beyond the fallacious idea that diseases of the mind either are not real or are shameful and to better recognize that the mind and the body are inextricably linked.

What Are the Lessons for the Future?

The central lesson is that of prevention. In future conflicts and peace-keeping actions, US troops will be exposed to myriad adverse physical factors, potentially including chemical warfare and biological warfare agents, as well as high levels of stress. Good baseline examinations will need to be done on service personnel prior to future deployment to form a basis for clinical and epidemiologic studies, and the Department of Defense is now developing plans for such evaluations. A recurrent problem in the epidemiologic studies of Gulf War veterans is that they have been mounted after the fact with little baseline data available. In addition, it will be important in the future to intervene proactively to prevent stress-related disorders. The Department of Defense has now deployed a Combat Stress Reduction Team with troops in Bosnia and plans to do so elsewhere in the future. While clearly these results need to be monitored, this direction is highly laudable and needs to be encouraged.

Physicians may expect to continue to see Persian Gulf War veterans as patients for many years to come. In some instances, we may identify specific diseases in these men and women, but in others, symptoms will remain ill defined, etiology will be imprecise, and disability will persist. However, despite the limitations of current epidemiologic studies and clinical investigations and regardless of the unanswered questions surrounding the hazards of potential exposures during the Persian Gulf War, these veterans will need all the resources and all of the care that they are owed by this nation that they have so generously and gallantly served.

Philip J. Landrigan, MD, MSc

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