Resolving the Gulf War Syndrome Question

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One central health question remains unanswered 7 years after the war with Iraq: Is there a "Gulf War syndrome"? Within a few months of returning home in 1991, some of the 750,000 Gulf War veterans from the United States, Great Britain, and Canada began complaining of fatigue, headaches, joint pains, sleep disturbances, cognitive difficulties, and other physical (somatic) symptoms (1). Approximately 1 year later, these diverse symptoms were conceptualized as a unique health problem, which has become the subject of intense scrutiny and controversy (2, 3).

Greater than 10 percent of veterans have been clinically evaluated for illnesses possibly related to service in the Persian Gulf (4–7). Most of the illnesses reported by veterans were found to be caused by well-known medical and psychologic conditions, but in about 20 percent of examinations, physical symptoms could not be definitely explained (5–7). Numerous assessments have suggested possible links between unexplained symptoms and various wartime health risks, including psychologic stress and exposure to chemical and biologic warfare agents, pesticides, pyridostigmine bromide prophylaxis, depleted uranium, oil well fire smoke, vaccinations, and endemic infectious diseases (7).

A series of six expert panels in the United States have analyzed available scientific data but did not identify a unique "Gulf War syndrome" (8–13). The inability to confirm a distinctive syndrome has generated much frustration among health care providers and researchers trying to aid Gulf War veterans and has led to both frustration and mistrust among veterans and their representatives, the media, and various review groups.

Several explanations have been offered for the failure to confirm a unique physical disease among Gulf War veterans with unexplained symptoms, despite extensive clinical and research efforts. An examination of these explanations illustrates how misconceptions about this health issue have slowed resolution of the "Gulf War syndrome" question.

Allegations of a cover-up are common responses to difficulties demonstrating a war-related syndrome. From the medical standpoint, this explanation is the least plausible because it is based on the premise that numerous private and government health professionals would participate in a conspiracy. In reality, a concerted clinical and research program has been established in three countries to identify the causes of veterans' illnesses and provide medical care (7, 14, 15). Physicians and researchers have had no incentive to hide the truth because whoever finds answers to these health questions will receive substantial professional recognition and personal gratification from helping veterans.

Another frequent explanation for the failure to demonstrate a "Gulf War syndrome" is that hazardous exposures have not been adequately investigated, either because wartime records are lacking or because of a delay in initiating research studies. This argument is based on the misconception that the identification of a new or previously unknown disease begins with epidemiologic studies of potential health risks rather than with careful examination of ill patients. As occurred at the beginning of the acquired immunodeficiency syndrome epidemic, unusual manifestations of disease first had to be evaluated by clinical examinations. Only after a unique disease process had been identified were epidemiologic studies conducted, not to find evidence of organic pathology but to evaluate risk factors for developing immune deficiency and to determine the spread of this new disease.

Viscerotropic leishmaniasis is another, more relevant example of disease identification because it is the one new disease that has been definitely linked to service in the Persian Gulf. Identification of 12 US Gulf War veterans with systemic Leishmania tropica infection was accomplished by clinically examining sick veterans and culturing parasites from biopsy samples (16). Epidemiologic studies of possible exposures were not necessary to identify this war-related health problem.

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If a unique organic disease eventually is demonstrated to be a cause of veterans’ illnesses, the lack of exposure records could hinder the assessment of risks among individual veterans. However, for the overall veteran population, the confirmation of a specific pathologic process probably would lead to the etiology. Once a distinctive disease is identified, the etiology either would be evident from current knowledge of human pathophysiology or could be identified by studying similar pathologic processes in animal models.

A third explanation for not confirming a war-related syndrome is that a better understanding is needed of the relation between psychologic stress and organic disease. A related argument is that stress in conjunction with various adverse wartime exposures has produced multiple diseases, rather than a single definable syndrome.

These explanations do not currently provide an answer for Gulf War health questions because physical abnormalities have not been consistently associated with veterans' somatic symptoms (5–7). In addition, an unidentified organic disease does not have to be postulated in order to explain somatic symptoms because stress and various psychologic conditions frequently present with fatigue, neurocognitive difficulties, sleep disturbances, and other physical complaints (17–19).

These misconceptions about the failure to identify a “Gulf War syndrome”—the possibility of a cover-up, inadequate study of risk factors, and the need to understand stress-induced pathology—have diverted attention from relevant clinical questions and available medical data. Clinical questions have to be addressed first in the evaluation of a possible new disease because the nature of the medical problem has to be determined. The four clinical registries, which have been established in the United Kingdom and Canada and in the United States by the Department of Veterans Affairs and Department of Defense, were therefore essential to assess veterans’ health concerns and have been decisive in defining their illnesses (20).

Beginning in 1992 with the Department of Veterans Affairs Gulf War health registry, more than 100,000 veterans have been evaluated in the four clinical programs and their specialized referral centers. Symptomatic veterans were found to be definitely ill with a wide diversity of health problems, but no indication of a new or previously unknown disease was identified, including a distinctive skin rash, neurologic deficit, immune disorder, or laboratory test abnormality (5–7).

Although not randomized studies, the systematic and intensive clinical examinations provided by the four registries have produced a massive amount of clinical data that must be considered when evaluating any hypothesis explaining veterans’ illnesses (11).

Because case series cannot be relied upon to provide conclusive answers, clinical case-control studies are the next step in the evaluation of veterans’ unexplained symptoms. Two case-control studies have identified indications of neurologic abnormalities among small groups of 14 and 23 ill veterans (21, 22), but other clinical studies have not found clear signs of neurologic pathology (23–27). Besides case-control studies, long-term medical follow-up of veterans is important to detect underlying pathology that may become apparent only after a disease has had time to progress. In the United States, clinical follow-up with updated medical findings is provided by the Department of Defense for active duty personnel and by the Department of Veterans Affairs for veterans who have left active service through its Persian Gulf health registry (as authorized by the US Congress and enacted in Public Law 102–585).

In addition to clinical studies, epidemiologic investigations of mortality and well-characterized illnesses are essential. These studies are helpful, even though they do not directly evaluate unexplained symptoms, because they determine whether any other aspect of veterans’ health has been adversely affected (15). Large-scale epidemiologic studies have so far found no overall increase in mortality or hospitalization rates from medical diseases and no overall increase in birth defects (28–30). As observed after prior wars, veterans have had increased rates of various psychologic conditions and stress-related symptomatology (13, 31).

Whereas investigations of well-defined illnesses are essential to assess veterans’ health, epidemiologic studies of an unidentified syndrome may not be as helpful. Observational (risk factor) studies are less likely to answer critical questions about a postulated new disease when a pattern of physical pathology is not detected because affected cases cannot be accurately identified. Specific case identification is not possible because common subjective complaints (e.g., fatigue, headache, arthralgias) do not provide sufficient information to reliably distinguish an unidentified disease from psychologic conditions, concurrent medical disorders, and the somatic distress that is prevalent in adult populations (32). The slow progress in defining and studying chronic fatigue syndrome illustrates this problem. Objective studies cannot be based exclusively on subjective criteria. Moreover, when cases of a postulated condition cannot be reliably identified, data derived from epidemiologic studies are difficult to interpret because of the unknown influence of illness misclassification, bias, chance findings, and confounding.
Well-designed epidemiologic surveys of Gulf War veteran populations have been conducted that included evaluations of self-reported symptoms and hazardous exposures (31, 33, 34). Although these studies provided valuable information, the findings based on subjective criteria require objective validation. Especially when recall bias may result from extensive news media coverage, independent confirmation is necessary (35).

Research studies of psychologic illnesses also can be criticized for utilizing subjective diagnostic criteria. However, valid results can be obtained from these studies because the defining characteristics of various psychologic conditions have been sufficiently established by extensive observations of human behavior and prior clinical studies.

The failure to identify a definite cause and remedy for veterans' health problems has raised doubts about the ability of mainstream medical science, with the aid of government, to answer important medical questions. Without conclusive answers for veterans' legitimate health concerns, a diversity of unverified syndromes and controversial health hazards have been offered as explanations (13). How can these disparate explanations be reconciled, along with numerous reports and medical findings? To resolve remaining Gulf War health questions, the focus has to be on testable hypotheses and peer-reviewed research.

In the investigation of psychologic factors, well-designed studies that use proven screening methods and clinical examinations to verify diagnoses are essential. Although there have been strong objections to the suggestion that the illnesses of some veterans may be due to stress, psychologic disorders have to be considered because they cause substantial suffering in all populations and effective treatments are available. In the search for physical causes of unexplained symptoms, progress depends on the demonstration of distinctive organic pathology and replication of this finding by physicians who are caring for Gulf War veterans. Without an objective standard to judge research results, hypotheses about causation and suggestive study findings may never be validated, regardless of how much funding and resources are committed.

REFERENCES


