

GAO

Report to the Chairmen and Ranking  
Minority Members of the Senate  
Committee on Armed Services and the  
House Committee on National Security

June 1997

# GULF WAR ILLNESSES

## Improved Monitoring of Clinical Progress and Reexamination of Research Emphasis Are Needed



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International Affairs Division

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June 23, 1997

The Honorable Strom Thurmond  
Chairman  
The Honorable Carl Levin  
Ranking Minority Member  
Committee on Armed Services  
United States Senate

The Honorable Floyd Spence  
Chairman  
The Honorable Ronald Dellums  
Ranking Minority Member  
Committee on National Security  
House of Representatives

Many of the approximately 700,000 veterans of the Persian Gulf War have complained of illnesses since the war's end in 1991. Some fear they are suffering from chronic disabling conditions because of wartime exposures to one or more agents with known or suspected health effects. This report responds to the mandate of the fiscal year 1997 defense authorization act that we analyze the effectiveness of the government's clinical care and medical research programs relating to illnesses that members of the armed forces might have contracted as a result of their service in the Gulf War.<sup>1</sup>

Specifically, we evaluated (1) the Department of Defense's (DOD) and the Department of Veterans Affairs' (VA) efforts to assess the quality of treatment and diagnostic services provided to Gulf War veterans and their provisions for follow-up of initial examinations, (2) the government's research strategy to study the veterans' illnesses and the methodological problems posed in its studies, and (3) the consistency of key official conclusions with available data on the causes of veterans' illnesses.

## Background

During their deployment associated with the Persian Gulf War, U.S. troops might have been exposed to a variety of potentially hazardous substances. These substances include compounds used to decontaminate equipment and protect it against chemical agents, fuel used as a sand suppressant in and around encampments, fuel oil used to burn human waste, fuel in

<sup>1</sup>Our response to the referenced legislation resulted in two additional studies: Defense Health Care: Medical Surveillance Has Improved Since the Gulf War, but Results in Bosnia Are Mixed (GAO/NSIAD-97-136, May 13, 1997) and a classified report issued earlier this year on biological agent defense.

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shower water, leaded vehicle exhaust used to dry sleeping bags, depleted uranium, parasites, pesticides, drugs to protect against chemical warfare agents (such as pyridostigmine bromide), and smoke from oil-well fires. DOD acknowledged in June 1996 that some veterans may have been exposed to the nerve agent sarin following the postwar demolition of Iraqi ammunition facilities.

Shortly after the war, some veterans began reporting health problems that they believed might be due to exposure to chemicals, pesticides, and other agents used during the war. Accordingly, both DOD and VA established programs through which Gulf War veterans could receive medical examinations and diagnostic services. From 1992 to 1994, VA participants received a regular physical examination with basic laboratory tests, and in 1994, VA established a standardized examination to obtain information about exposures and symptoms related to diseases endemic to the Gulf region and to incorporate specific tests to detect the "biochemical fingerprints" of certain diseases. If a diagnosis was not apparent, the standard examination protocols provided for up to 22 additional tests and provided for additional specialty consultations. If the illness defied diagnosis, VA registrants might have been sent to one of four VA Persian Gulf referral centers.

DOD initiated its Comprehensive Clinical Evaluation Program in June 1994. It was primarily intended to provide diagnostic services similar to the VA program and employed a similar clinical protocol. However, the VA program was among the first extensive efforts to gather data from veterans regarding the nature of their problems and the types of hazardous agents to which they might have been exposed. (See app. I for details.)

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## Results in Brief

Our review found that (1) although efforts have been made to diagnose veterans' problems and care has been provided to many eligible veterans, neither DOD nor VA has systematically attempted to determine whether ill Gulf War veterans are any better or worse today than when they were first examined; (2) while the ongoing epidemiological research will provide descriptive data on veterans' illnesses, formidable methodological problems are likely to prevent researchers from providing precise, accurate, and conclusive answers regarding the causes of veterans' illnesses; and (3) support for some official conclusions regarding stress, leishmaniasis, and exposure to chemical agents was weak or subject to alternative interpretations.

Over 100,000 of the approximately 700,000 Gulf War veterans have participated in DOD and VA health examination programs established after the war. Based on the examinations and reports provided by DOD and VA, nearly 90 percent of the examined veterans are symptomatic, reporting a wide array of health complaints and disabling conditions. While VA and DOD health examination programs have sought to evaluate these veterans' problems and refer eligible veterans for further care, neither DOD nor VA currently has mechanisms in place to determine whether these ill veterans are any better or worse today than when they were first examined. Both agencies have tried to measure or ensure the quality of veterans' initial examinations. While some measures of quality are in place for military or VA health care in general, neither agency can now determine the appropriateness or effectiveness of the treatment received by ill Gulf War veterans.<sup>2</sup>

Federal research on Gulf War veterans' illnesses has not been pursued proactively. Although these veterans' health problems began surfacing in the early 1990s, the vast majority of research was not initiated until 1994 or later. And, much of this research was associated with legislation or external reviewers' recommendations. Thus, although at least 91 studies have received federal financial support, about four-fifths of the funded studies are not complete, and certain studies will not be available until after 2000. Some hypotheses (for example, that veterans' current symptoms are due to stress) were pursued earlier and more aggressively than others (for example, that symptoms are due to low-level exposure to chemical warfare agents), and some hypotheses that were initially unfunded by the federal government (for example, that symptoms are due to the delayed chronic effects of exposure to organophosphates,<sup>3</sup> which were in pesticides used in the Gulf) were pursued with private sector funding. In recent years, VA and DOD have significantly broadened their research programs, to include efforts to seek external advice.

Without accurate exposure information, the investment of millions of dollars in further epidemiological research on the risk factors (or potential causes) for veterans' illnesses may result in little return. The government's research has primarily involved epidemiological studies, most of which focus on the nature and prevalence of the veterans' symptoms and illnesses or the identification of causes for the illnesses. While mortality

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<sup>2</sup>We are conducting further work addressing medical care provided to Gulf War veterans. See VA Health Care: Observations on Medical Care Provided to Persian Gulf Veterans (GAO/T-HEHS-97-158, June 19, 1997).

<sup>3</sup>Organophosphates are a class of chemicals found in some pesticides and chemical warfare agents.

information and data on the prevalence of various problems may be valuable, because of formidable methodological problems facing investigators, epidemiological research on Gulf War veterans' illnesses will not be able to provide precise, accurate, and conclusive answers regarding the causes of veterans' illnesses. Specifically, studies generally are hampered by the lack of (1) accurate, person-based, dose-specific exposure data; (2) known biological markers (such as detectable antibodies to specific agents or diseases); and (3) specific case definition (definition of particular syndromes or clusters of symptoms to study).

While some prevalence data may be useful, we agree with the Institute of Medicine and the Presidential Advisory Committee on Gulf War Veterans' Illnesses.<sup>4</sup> that population-based comparisons that group together veterans with varied exposures may mask higher rates of illness among veterans with specific exposure histories. The plans for toxicological research on the health effects of low-level exposures to various agents will be useful in efforts to determine whether veterans' current unexplained symptoms or conditions are consistent with such exposure. To date, the research program has not included an assessment of the clinical progress of ill Gulf War veterans, which is critical to identifying the appropriateness and effectiveness of their treatment and could be useful to provide direction to the research agenda.

Six years after the war, little is conclusively known about the causes of Gulf War veterans' illnesses. Not only were few strong, conclusive statements made in the executive branch reports we reviewed, but support was weak or subject to alternative interpretation for three conclusions made by the Presidential Advisory Committee and endorsed by DOD. In addition, two questions remain unresolved.

First, the Committee concluded that stress is likely to be an important contributing factor to the broad range of illnesses currently being reported by Gulf War veterans and that studies have found higher rates of posttraumatic stress disorder (PTSD) in Gulf War veterans. However, the link between stress and these veterans' physical symptoms is not well established in the evidence the Committee cited, and the reported prevalence of PTSD among Gulf War veterans may be overestimated because of problems in the methods used in studies to identify it (for example, there were frequent failures to exclude physical causes for

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<sup>4</sup>See Presidential Advisory Committee on Gulf War Veterans' Illnesses, Final Report (Washington, D.C.: GPO), December 1996.

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veterans' symptoms or to conduct structured clinical interviews, which are necessary components of PTSD diagnosis).

Second, based on a small number of diagnosed cases, VA and DOD concluded that the likelihood of leishmania tropica (a parasite) as an important risk factor for widely reported illness has diminished and the Committee found it unlikely to be "responsible for long term health effects in Gulf War veterans." However, the extent of asymptomatic leishmania infection is unknown, and the possibility of prolonged latency and apparent clinical dormancy (up to 20 years) of an infection that may reemerge in the presence of immune deficiency underscores the need to retain leishmania among the potential risk factors.

Third, the Committee concluded that it was unlikely that the health effects reported by Gulf War veterans are the results of exposure to organophosphate or mustard chemical warfare agents, even though there is substantial evidence that organophosphate compounds might be associated with delayed or long-term health effects similar to those experienced by the Gulf War veterans.

Unresolved questions concern the extent to which veterans may have been exposed to (1) chemical agents as a result of fallout from the destruction of suspected chemical weapons storage sites and (2) the biological agent aflatoxin, the health effects of which may not be known for months, or even years, after exposure.

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## DOD and VA Have No Systematic Approach to Monitoring Gulf War Veterans' Health After Initial Examination

DOD and VA officials have testified that whatever uncertainties may exist about the cause of Gulf War veterans' illnesses, the veterans are receiving appropriate and effective symptomatic treatment. However, DOD and VA have no mechanism to monitor the quality, appropriateness, or effectiveness of care provided to Gulf War veterans after their initial examination. Furthermore, DOD and VA officials said they had no plans to establish a mechanism to monitor these veterans' progress. This monitoring and follow-up is important not only to ensure that diagnosed conditions are properly treated but also because (1) undiagnosed signs and symptoms are not uncommon among ill veterans, (2) treatment for veterans with undiagnosed conditions is based on their symptoms, and (3) veterans with undiagnosed conditions or multiple diagnoses may see multiple providers. These agencies have relied on such mechanisms as training and standards for physician qualification, which may not be sufficient to ensure a given level of effectiveness for the care provided or

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do not permit identification of the most effective treatments.<sup>4</sup> In contrast, some steps have been taken to monitor quality and patient satisfaction with veterans' initial registry examinations. (See app. II for details.)

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## Federal Research Strategy Lacks a Coherent Approach

The bulk of ongoing federal research currently focuses on the epidemiological study of veterans' illnesses. While this approach may yield descriptive data on veterans' mortality and general health profiles, methodological problems facing government epidemiological research on Gulf War veterans' illnesses will severely limit its ability to identify the potential causes of the illnesses. Initially, the government was not proactive in acknowledging and collecting data on the factors that might have caused Gulf War veterans' health problems, and the research agenda was not articulated until several years after the war ended.

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## Delays and Focus of Federal Research Are Hindering Outcomes

Our review of research projects and interviews with agency officials showed that the vast majority of federal research was not initiated until 1994. This 3-year delay has complicated the task facing researchers. In addition, it has limited the amount of completed research currently available. Of the 91 federally sponsored studies, 72 were ongoing when we reviewed them in early 1997, and some of the studies will not be complete until 2000 or later.

The focus of federal research has primarily been the epidemiological study of the prevalence and cause of Gulf War illnesses rather than the diagnosis, treatment, and prevention of them. With respect to determining the causes, researchers will likely continue to find it difficult to detect effects of particular wartime exposure and to eliminate alternative explanations for Gulf War veterans' illnesses because of the absence of valid and reliable data on exposures and the multiplicity of agents to which the veterans were exposed. Data on the prevalence of various health problems can be useful but requires careful interpretation in the absence of better information on the factors to which veterans were exposed. While multiple studies of the role of stress in the veterans' illnesses have been supported with federal research dollars, basic toxicological questions regarding the substances to which they were exposed remain unanswered. Finally, there is an absence of efforts to measure Gulf War veterans' clinical progress. This leaves the government unable to promptly determine the quality and effectiveness of treatments

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<sup>4</sup>See VA Health Care: Observations on Medical Care Provided to Persian Gulf Veterans (GAO/T-HEHS-97-158, June 19, 1997).

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currently being provided to Gulf War veterans or to use this information when funding additional clinical research.

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### Methodological Problems Limit the Effectiveness of Ongoing Epidemiological Research

Federal researchers studying Gulf War illnesses have faced a number of challenges and encountered significant problems in linking exposures or potential causes to observed illnesses or symptoms.

- Researchers have found it extremely difficult to gather information about unplanned exposures in the Gulf to such things as oil fire smoke and insects carrying infection, and DOD has acknowledged that records of the use of pyridostigmine bromide and vaccinations to protect against chemical/biological warfare exposures were inadequate.
- Gulf War veterans were typically exposed to a wide array of agents, making it difficult to isolate and characterize the effects of individual agents or to study their combined effects.
- Most epidemiological studies have relied only on self-reports for measuring most of the agents to which veterans may have been exposed during the Gulf War.
- The passage of time following these exposures has made it increasingly difficult to have confidence in any information gathered about them through retrospective questioning of veterans. Reliance on self-reporting to assess exposures has two problems. Veterans' recall after such a long time period may be inaccurate or biased. Moreover, there is often no straightforward way to test the validity of self-reported exposure information, making it impossible to separate bias in recalled information from actual differences in the frequency of exposures. As a result, findings from these studies may be spurious or equivocal.
- Classifying the symptoms and identifying illnesses of Gulf War veterans have been difficult. From the outset, symptoms reported by veterans have been varied and difficult to classify into one or more distinct illnesses. Moreover, several different diagnoses might provide plausible explanations for some of the specific health complaints. It has thus been difficult to develop a case definition (that is, a reliable way to identify individuals with a specific disease), which is a criterion for doing effective epidemiological research.

Appendix III provides more detailed information on the nature and extent of the federal government's research efforts.



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## Support for Key Government Conclusions Is Weak or Subject to Alternative Interpretations

In the absence of official conclusions from DOD and VA, we examined conclusions drawn in December 1996 by the Presidential Advisory Committee on Gulf War Veterans' Illnesses, which was established by the President to review the activities of the executive branch regarding Gulf War veterans' illnesses. In January 1997, DOD endorsed the Committee's conclusions about the likelihood that exposure to 10 commonly cited agents contributed to the explained and unexplained illnesses of these veterans. We found that the evidence to support several of these conclusions is either weak or subject to alternative interpretations.

The Committee concluded that "stress is likely to be an important contributing factor to the broad range of illnesses currently being reported by Gulf War veterans." While stress can induce physical illness, the link between stress and these veterans' physical symptoms has not been firmly established by the evidence the Committee cited. For example, a large-scale, federally funded study concluded that "for those veterans who deployed to the Gulf War and currently report physical symptoms, neither stress nor exposure to combat or its aftermath bear much relationship to their distress." The Committee has stated that "epidemiological studies to assess the effects of stress invariably have found higher rates of posttraumatic stress disorder (PTSD) in Gulf War veterans than among individuals in nondeployed units or in the general U.S. population of the same age." Our review indicated that the prevalence of PTSD among Gulf War veterans may be overestimated due to problems in the methods used to identify it. Specifically, the studies on PTSD to which the Committee refers have not excluded other conditions, such as neurological disorders that produce symptoms similar to PTSD and can also elevate scores on key measures of PTSD. We also believe that the use of broad and heterogeneous groups of diagnoses (e.g., "psychological conditions" — ranging from tension headache to major depression) in reporting data from DOD's clinical program may contribute to overestimation of the extent of serious psychological illnesses among Gulf War veterans.

The Committee also concluded that "it is unlikely that infectious diseases endemic to the Gulf region are responsible for long term health effects in Gulf War veterans, except in a small known number of individuals." Similarly, the Persian Gulf Veterans Coordinating Board (PGVCB)<sup>5</sup> concluded that because of the small number of reported cases, "the likelihood of *Leishmania tropica* as an important risk factor for widely reported illness has diminished." While this is the case for observed

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<sup>5</sup>The PGVCB, comprised of the Secretaries of Defense, Veterans Affairs, and Health and Human Services, is charged with coordinating the federal response to Gulf War veterans' illnesses.

symptomatic infection with the parasite, the prevalence of asymptomatic infection is unknown, and such infection may reemerge in cases in which the patient's immune system becomes deficient. However, as the Committee has noted, the infection may remain dormant up to 20 years. Because of this long latency and the lack of widely available screening methods, the infected population is hidden, and because even classic forms of Leishmaniasis are difficult to recognize, we believe that Leishmania should be retained as a potential risk factor for individuals who suffer from immune deficiency.

The Committee also concluded that it is unlikely that the health effects reported by many Gulf War veterans were the result of (1) biological warfare agents, (2) chemical warfare agents, (3) depleted uranium, (4) infectious diseases endemic to the region, (5) oil-well fire smoke, (6) pesticides, (7) petroleum products, (8) pyridostigmine bromide, or (9) vaccines. However, our review of the conclusions made by the Committee indicated the following:

- While the government found no evidence that biological weapons were deployed, during the Gulf War, the United States did not deploy a real-time biological warfare agent detection system during the war, and the effects of one agent, aflatoxin, would not be observed for many years.
- Evidence from various sources indicates that chemical agents were present at Khamisiyah, Iraq, and elsewhere on the battlefield. The magnitude of the exposure to chemical agents has not been fully resolved. As we have previously noted, "available bomb damage assessments during the war concluded that 16 of 21 sites categorized by Gulf War planners as nuclear, biological, and chemical (NBC) facilities had been successfully destroyed. However, information compiled by the United Nations Special Commission (UNSCOM) since the end of Desert Storm reveals that the number of suspected NBC targets identified by U.S. planners, both prior to and during the campaign, did not fully encompass all the possible NBC targets identified by U.S. planners. UNSCOM has conducted investigations at a large number of the facilities suspected by the U.S. authorities as being NBC related. Regarding the few suspected chemical weapon sites that have not yet been inspected by UNSCOM, we have been able to determine that each was attacked by coalition aircraft during Desert Storm and that one site is located within the Kuwait theater of operation in close proximity to the border, where coalition ground forces were located. However, we have yet to learn why these facilities have not been investigated."<sup>6</sup>

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<sup>6</sup>Operation Desert Storm: Evaluation of the Air Campaign (GAO/NSIAD-97-134, June 12, 1997), p. 2.

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- Exposure to certain organophosphates can induce a delayed neurological condition without causing immediate symptoms.
  - Available research indicates that exposure to combinations of pyridostigmine bromide and other chemicals used during the Gulf War can cause damaging health effects greater than to these agents individually.

(See app. IV for details.)

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## Recommendations

Because of the numbers of Gulf War veterans who continue to experience illnesses that may be related to their service during the Gulf War, we recommend that the Secretary of Defense, in conjunction with the Secretary of the Department of Veterans Affairs, (1) develop and implement a plan to monitor the clinical progress of Gulf War veterans in order to help promote appropriate and effective treatment and provide direction to the research agenda and (2) give greater priority to research on treatment for ill veterans and on low-level exposures to chemicals and their interactive effects and less priority to further epidemiological studies. We also recommend that the Secretaries of Defense and Veterans Affairs refine the current approaches of the clinical and research programs for diagnosing posttraumatic stress disorder consistent with suggestions recently made by the Institute of Medicine, which noted the need for improved documentation of screening procedures and patient histories (including occupational and environmental exposures) and the importance of ruling out alternative causes of impairment.

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## Agency Comments and Our Evaluation

We obtained comments on a draft of this report from DOD, VA, and the Presidential Advisory Committee on Gulf War Veterans' Illnesses. DOD partially concurred with the report, indicating that the thrust of the recommendations had merit but did not fully take into account the complex set of health outcomes related to the war and did not recognize DOD's accomplishments. DOD also noted that our findings differed from those of the Institute of Medicine and the Committee and commented that we had not carried out the same level of careful and thoughtful assessment as had those committees.

VA commented that although some aspects of our report have merit, our recommendations reflected a lack of understanding of clinical research, epidemiology, and toxicology. VA indicated that (1) the creation of a new database was not likely to provide accurate and valid assessment of these Gulf War veterans' health status; (2) DOD and VA are already giving greater

priority to research on low-level exposures to chemicals, but do not want to give less priority to epidemiological research; and (3) VA was already making efforts to improve current approaches to PTSD and other stress-related disorders.

The Presidential Advisory Committee commented that our draft contained factual errors, did not provide references or citations to scientific literature, lacked substantiation and analytic rigor, and should not be issued in its current form. The Committee was particularly concerned with our finding that the support or evidence it had for some of its conclusions was weak.

None of the comments we received provide evidence to challenge our principal findings and conclusions that (1) DOD and VA have no means to systematically determine whether symptomatic Gulf War veterans are better or worse today than when they were first examined and (2) ongoing epidemiological research will not provide precise, accurate, and conclusive answers regarding the causes of the Gulf War veterans' illnesses. All of the comments we received seek to shift the onus of identifying and substantiating the causes of Gulf War illnesses to us, when in fact we merely reviewed the sufficiency and persuasiveness of the evidence behind the administration's conclusions. In some instances, we found it to be weak or open to alternative interpretation. We believe the burden of proof is still on those who have made the assertions about the likely and unlikely causes of the illnesses.

Nevertheless, in light of the comments we received, we have added more citations to the scientific support and documentation and modified the language in the text to clarify our position so that other readers will not misconstrue the meaning of our report. We also double-checked the information that was challenged in the comments we received and found that the data as originally presented was correct. Therefore, the thrust of our message remains unchanged.

Our point-by-point evaluation of the detailed comments provided by DOD, VA, and the Committee are provided in appendixes V-VII. However, because the Committee's comments were the most strident, our evaluation of its key points is summarized as follows.

Regarding stress, the Committee states that we ignored its analytical approach, which was to compare the "known health effects of the risk factor to the symptoms reported by Gulf War veterans." We found,

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however, that the Committee offered little evidence that stress was an important contributor of the "broad range" of veterans' symptoms. Given the nonspecific nature of the health effects associated with stress, almost any pattern of symptoms and illnesses would be compatible with it, making it difficult to scientifically test the hypothesis posed by the Committee's approach (that the pattern of veterans' illnesses is consistent with the known effects of stress). Although the Committee notes that scores on PTSD screening questionnaires are higher among Gulf veterans than among controls, confirmatory psychiatric interviews to eliminate alternative explanations for elevated PTSD screening scores were generally not done.

Because we questioned the Committee's support for its conclusion that the likelihood of Leishmania infection has diminished as an explanation for widespread illness, the Committee sought to transfer the burden of proof to us by asking that we justify any continued concern about asymptomatic infection. We found that the Committee's justification for dismissal of Leishmania as a risk factor rests heavily on two ill-supported assumptions: (1) that diagnostic programs have been highly likely to detect the disease, even in the absence of any widely available screening or diagnostic tests and in the presence of nonspecific symptoms, and (2) that the course of various forms of leishmaniasis is well understood by scientists and by the doctors examining the veterans. Insofar as the prevalence of this infection is still unknown and it is impossible to predict which veterans' immune systems will be weakened, and given the inability to identify this hidden population in the absence of a valid screening test, we believe it is premature to discount leishmania as a risk factor.

Finally, regarding our evaluation of the Committee's conclusion that low-level exposures to chemicals such as pesticides are unlikely to be associated with veterans' health conditions, the Committee appears not to contest the fact that laboratory data document specific health effects in animals exposed to one or more organophosphate agents that are not detectable in the usual clinical tests. We find it difficult to reconcile the Committee's dismissal of such exposure as an "unlikely" cause of veterans' health problems with its acknowledgement of an absence of data on an important exposure scenario. Moreover, where the Committee apparently found no data to suggest a problem with low-level exposures, we found some data that do pose concerns. While the Committee argues that these studies were done on animals, they are consistent with standard toxicological practice employed by the Environmental Protection Agency and others. The Committee's insistence that such effects be demonstrated

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in humans appears unreasonable, as exposing humans to toxic substances for experimental research cannot be done for obvious ethical reasons. Also, while the study of occupational or accidental exposures, such as the sarin exposures that occurred in Japanese terrorist incidents, may provide some degree of information, the value of such information is generally limited by the poor description of the actual levels of the exposure in the case of accidents, the limited range of exposures (in the case of occupational use), or the lack of comparability with the circumstance in question. The hypotheses derived from such study would thus require confirmation and testing in controlled experimental settings.

DOD provided two sets of comments, which we have reprinted in appendix V. We responded to DOD's second set of comments, received on June 17, 1997, by incorporating appropriate changes in our report. VA and the Presidential Advisory Committee's comments are reprinted in appendixes VI and VII, respectively.

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## Scope and Methodology

To address our first objective—the extent of DOD's and VA's clinical follow-up and monitoring of treatment and diagnostic services—we reviewed literature and agency documents and conducted structured interviews with DOD and VA officials managing the respective agencies' registries for Persian Gulf War veterans that requested postwar evaluations. We asked questions designed to identify and contrast their methods for monitoring the quality and outcomes of their treatment and diagnostic programs and the health of the registered veterans.

The second objective concerns the government's research strategy to study the veterans' illnesses and the methodological problems posed in its studies. To answer this question we conducted a systematic review of pertinent literature and agency documents and reports, including reports issued by the Presidential Advisory Committee and the Institute of Medicine. We also interviewed representatives of PCVCB's Research Working Group and officials of VA and DOD. We surveyed primary investigators of ongoing epidemiological studies. We also collected data on project expenditures by fiscal year but did not attempt to independently verify these figures.

Because different methodological standards apply to various types of research and because the overwhelming majority of federally sponsored research is categorized as epidemiological, we limited our survey of investigators to those responsible for ongoing epidemiological studies.

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With an expert epidemiological consultant, we devised a questionnaire to assess critical elements of these studies (including the quality of exposure measurement, specificity of case definition, and steps to ensure adequate sample size) and to identify specific problems that the primary investigators may have encountered in implementing their studies. Of the 43 ongoing epidemiological studies identified by PGVCB in the November 1996 plan, we interviewed primary investigators for 31 (72 percent). We also reviewed and categorized descriptions of all 91 projects identified by April 1997, based on their apparent focus and primary objective. Finally, to review the progress of major ongoing research efforts, we visited the Walter Reed Army Institute of Research, the Naval Health Research Center, and two of VA's Environmental Hazards Research Centers.

To address the third objective, we reviewed major conclusions of the PGVCB and the Presidential Advisory Committee to determine the strength of evidence supporting these conclusions. The purpose of this review was not to critique PGVCB's or the Presidential Advisory Committee's efforts, per se, but rather to describe the amount of knowledge about Gulf War illnesses that has been generated by research 6 years after the war. We reviewed these conclusions because they were the strongest statements that we had come across on these matters by any official body. The Presidential Advisory Committee's report was significant because the panel included a number of recognized experts in the scientific questions at issue who were assisted by a large staff of scientists and attorneys. In addition, the Committee conducted an extensive review of the research. Thus, evaluating these conclusions provided important evidence about how fruitful the federal research had been thus far. To address this objective, we reviewed scientific literature cited by the Presidential Advisory Committee as well as others. We also consulted experts in the fields of epidemiology, toxicology, and medicine and interviewed officials of DOD, VA, and the Central Intelligence Agency. We checked our own interpretation of key study findings with the authors and had independent experts review our draft report.

Because of the scientific and multidisciplinary nature of this issue, we ensured that staff conducting the work had appropriate backgrounds in the fields of epidemiology, statistics, psychology, environmental health, toxicology, engineering, weapon design, and program evaluation and methodology. In addition, we used in-house expertise in chemical and biological warfare and in military and veterans health care systems. Also, experts who reviewed our work had backgrounds in medicine, public health, and research methods. Moreover, we held extensive discussions

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with experts in academia in each of the substantive fields relevant to this issue.

Our work was completed between October 1996 and April 1997 in accordance with generally accepted government auditing standards.

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We are sending copies of this report to other interested congressional committees; the Secretaries of Defense, Veterans Affairs, and Health and Human Services; the Chair of the Presidential Advisory Committee; and other interested parties. We will make copies available to others upon request.

If you have any questions or would like additional information, please contact me at (202) 512-3092 or Sushil K. Sharma, Ph.D, Dr.P.H., Assistant Director, at (202) 512-3460. Major contributors to this report are listed in appendix VIII.

A handwritten signature in black ink, appearing to read 'Kwai-Cheung Chan', with a long horizontal flourish extending to the right.

Kwai-Cheung Chan  
Director, Special Studies and Evaluations



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**Abbreviations**

CARC	Chemical agent resistant coating
CCEP	Comprehensive Clinical Evaluation Program
CDC	Centers for Disease Control
CIA	Central Intelligence Agency
DEET	N,N-diethyl-m-toluamide
DOD	Department of Defense
DS2	Decontaminating solution 2
HHS	Department of Health and Human Services
IOM	Institute of Medicine
NBC	Nuclear, Biological, and Chemical
NHRC	Naval Health Research Center
OPIDN	Organophosphate-induced delayed neuropathy
PAC	Presidential Advisory Committee on Gulf War Veterans' Illnesses
PGHREP	Persian Gulf Health Registry Examination Program
PGVCB	Persian Gulf Veterans Coordinating Board
PTSD	Posttraumatic stress disorder
UNSCOM	United Nations Special Commission on Iraq
USAMRIID	U.S. Army Medical Research Institute of Infectious Diseases
VA	Department of Veterans Affairs
WRAIR	Walter Reed Army Institute of Research
WRAMC	Walter Reed Army Medical Center

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# Government Health and Research Programs for Gulf War Veterans

In the aftermath of the Persian Gulf War, which ended on February 28, 1991, many veterans have experienced illnesses that they believe they contracted while in the Gulf due to exposures to hazardous materials or chemical and biological warfare agents. The Department of Veterans Affairs (VA) and the Department of Defense (DOD) later initiated health programs offering physical examinations and diagnostic services to these veterans. As it became apparent that the symptoms and causes of these illnesses varied widely and the illnesses were difficult to diagnose, the government began to research the reasons for the veterans' health problems.

## U.S. Troops' Exposure to Hazardous Substances

During their service in the Gulf, U.S. troops were reportedly exposed before, during, and after the war to a variety of potentially hazardous substances. These include decontaminating and protective compounds (particularly decontaminating solution 2, or DS2, and chemical agent resistant coating (CARC)), diesel fuel used as a sand suppressant in and around encampments, fuel oil used to burn human waste, fuel in shower water, and leaded vehicle exhaust used to dry sleeping bags. For example, as we reported to staff of the House Subcommittee on Oversight and Investigations in 1994, DS2 was to be widely distributed among Army units and equipment in Saudi Arabia, though the Army did not know how much or where the solution was distributed. The potential effects of DS2 on humans include mild or severe burns, corrosion to tissues of the skin or eye, liver damage, and adverse reproductive effects.<sup>7</sup> Other potential hazards associated with Gulf service included infectious diseases (most prominently leishmaniasis, a parasitic infection), the use of pyridostigmine bromide and vaccines (to protect against chemical and biological weapons), depleted uranium (contained in certain ammunition and in the fragments of exploded rounds), pesticides and insect repellents, chemical and biological warfare agents, and compounds and particulate matter contained in the extensive smoke from the oil-well fires at the end of the war.

Shortly after the war, some veterans began reporting health problems that they believed might be due to their participation in the war. As we noted in May 1995, the 123rd Army Reserve Unit in Indiana reported unexpected signs and symptoms that could not easily be explained.<sup>8</sup> Veterans in other

<sup>7</sup>Also see *Hazardous Materials: DOD Should Eliminate DS2 From Its Inventory of Decontaminants* (GAO/NSIAD-90-10, Apr. 25, 1990).

<sup>8</sup>*Operation Desert Storm: Health Concerns of Selected Indiana Persian Gulf War Veterans* (GAO/HEHS-95-102, May 1995).

units began to report similar symptoms that also could not be easily explained. Many veterans reported exposure to chemicals, pesticides, and other agents, such as vaccines and pyridostigmine bromide, as possible causes of their illnesses.

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## Health Examination Programs for Gulf War Veterans

Consistent with the Veteran's Health Care Act of 1992, both VA and DOD have established programs through which they provide medical examination and diagnostic services, free of charge, to Gulf War veterans. The VA launched its Persian Gulf Health Registry Examination Program (PGHREP) in 1992, and DOD initiated the Comprehensive Clinical Evaluation Program (CCEP) in June 1994. PGHREP is currently available at most VA medical centers, and DOD's CCEP examinations are available at 148 sites worldwide.<sup>9</sup>

Initially, PGHREP participants received a regular physical examination with basic laboratory tests. However, in 1994, VA established a standardized examination to (1) obtain information about symptoms and exposures; (2) call the clinician's attention to diseases endemic to the Gulf region; and (3) direct baseline laboratory studies, including a chest X-ray (if one has not been done recently), blood count, urinalysis, and blood chemistry and enzyme analyses for detection of certain diseases. If a diagnosis is not apparent, facilities follow the clinical evaluation protocol originally developed for VA's referral centers and now used in VA and military medical centers nationwide. The examination protocol suggests 22 additional baseline tests and additional specialty consultations, from which further diagnostic procedures may be considered, depending on the veteran's symptoms. If the illness cannot be diagnosed, a VA registrant may be referred to one of four VA Persian Gulf Referral Centers located in Washington, D.C.; Houston, Texas; Los Angeles, California; and Birmingham, Alabama.

Although these registry programs are primarily intended to provide diagnostic services, the VA's registry program, in particular, was among the first extensive efforts to gather data from veterans regarding the nature of their problems and the types of factors to which they might have been exposed. However, during the first 2 years of the PGHREP's operation, when exposure and symptom information was freshest in most respondents'

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<sup>9</sup>A declining proportion of Gulf War veterans are covered by military medical health services. Thus, an increasing number would be eligible only for VA care, and some portion have access to neither VA nor DOD health care services apart from the PGHREP and CCEP examination programs. It is important to note that receipt of a VA registry examination does not entail eligibility for free treatment of any conditions detected.

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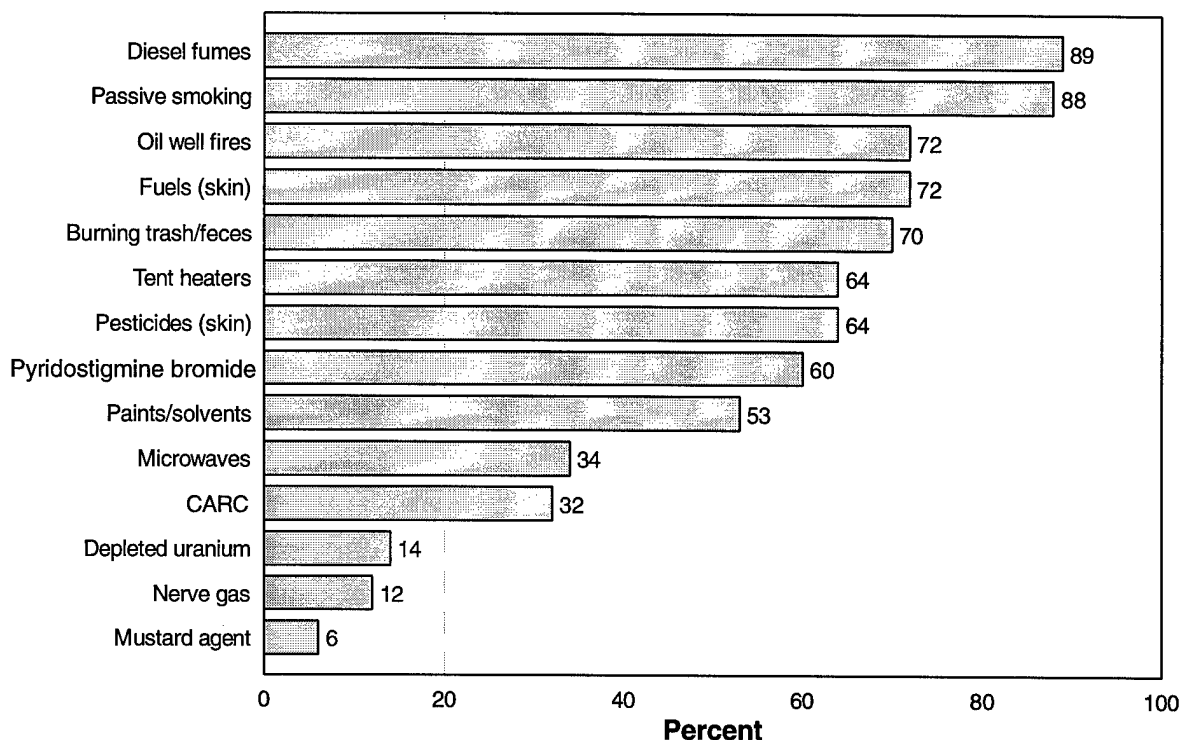
memory, efforts to collect data on symptoms and self-reported exposure(s) were more limited in scope.

In February 1997, the VA reported its analysis of the self-reported exposures to hazardous substances identified by the 3,181 veterans who registered after the VA revised its data collection forms. Although interpreting such information is difficult due to self-selection of registry participants and problems with retrospective reporting based on recall, many veterans reported exposure to multiple substances. VA reported that 89 percent of these registered veterans believed they had been exposed to diesel or other petrochemical fumes, 88 percent to passive smoking, 72 percent to smoke from oil fires, 72 percent to skin exposure to fuel, 70 percent to burning trash/feces, 64 percent to smoke from tent heaters, 64 percent to pesticides in cream or spray form, 60 percent to pyridostigmine bromide, 53 percent to paints or solvents, 34 percent to microwaves, 32 percent to CARC, 14 percent to depleted uranium, 12 percent to nerve gas, and 6 percent to mustard gas.<sup>10</sup> (See fig. I.1.) As of June 1996, DOD acknowledged the potential exposure of some veterans to the nerve agent sarin following the postwar U.S. demolition of Iraqi ammunition facilities.

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<sup>10</sup>H. Kang et al., "A Review of the Department of Veterans Affairs Revised Persian Gulf Registry and In-Patient Treatment Files" (Washington, DC: VA Environmental Epidemiology Service, Feb. 1997), table 17.

Figure I.1: Percent of 3,181 VA Registrants That Reported Having Been Exposed to Various Agents During the Gulf War



Source: Data provided in H. Kang et al., "A Review of the Department of Veterans Affairs Revised Persian Gulf Registry and Inpatient Treatment Files" (Washington, D.C.: VA Environmental Epidemiology Service, Feb. 1997), table 17.

## Government Research Program

In addition to providing examination services, in the 6 years since the end of the Gulf War, the federal government, primarily through DOD and VA, has sponsored a variety of research on Gulf War veterans' illnesses. DOD research is one component of a broader agenda coordinated under the aegis of the Persian Gulf Veterans' Coordinating Board (PGVCB), which comprises the Secretaries of the Department of Health and Human Services (HHS), VA, and DOD. The details of this agenda are described in the PGVCB publication entitled A Working Plan for Research on Persian Gulf Veterans' Illnesses, first published in 1995 and revised in November 1996.<sup>11</sup>

<sup>11</sup>A Working Plan for Research on Persian Gulf Veterans' Illnesses (First Revision)," Department of Veterans Affairs, November 1996.



This agenda was developed in response to an Institute of Medicine (IOM) conclusion that

“the DOD and VA should determine the specific research questions that need to be answered. Epidemiologic studies should be designed with the objective of answering these questions given the input of experts in epidemiologic research methods and data analysis, along with the input of experts in the subject matter areas to be investigated.”

Accordingly, most of the research sponsored under this agenda is characterized by PGVCB as epidemiological.

The objectives of epidemiologic study are to determine the extent of disease in the population, the causes of disease and its modes of transmission, the natural history of disease, and the basis for developing preventive strategies or interventions.<sup>12</sup>

To conduct such studies, investigators must follow a few basic, generally accepted principles. First, they must specify diagnostic criteria to (1) reliably determine who has the disease or condition being studied and who does not and (2) select appropriate controls (people who do not have the disease or condition).

Second, the investigators must have valid and reliable methods of collecting data on the past exposure(s) of those in the study to possible factors that may have caused the symptoms. The need for accurate, dose-specific exposure information is particularly critical when low-level or intermittent exposure to drugs, chemicals, or air pollutants is possible. It is important not only to assess the presence or absence of exposure but also to characterize the intensity and duration of exposure. To the extent that the actual exposure of individuals is misclassified, it is difficult to detect any effects of the exposure. Another means of linking environmental factors to disease is to determine whether or not there is evidence that as the exposure increases, the risk of disease also increases. However, this dose-response pattern can be detected only if the degree of exposure among different groups can be determined.

Finally, in addition to specific case definition and dose-specific exposure information with known accuracy, it is important that a sufficient number of persons be studied to have a reasonable likelihood of detecting any

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<sup>12</sup>A. M. Lilienfeld and D. E. Lilienfeld, *Foundations of Epidemiology* (New York: Oxford University Press, 1980); L. Goodis, *Epidemiology* (Philadelphia, PA: W. B. Saunders Company, 1996); and D. E. Lilienfeld and P. D. Stolley, *Foundations of Epidemiology* 3rd ed. (New York: Oxford University Press, 1994).

relationship between exposures and disease. To the extent that this relationship is subtle or obscured by loose case definition (that is, a case definition that is too broad and encompasses different types of illnesses) or problems in measuring exposure, larger samples would be required. For example, the IOM has noted that

“very large groups must be studied in order to identify the small risks associated with low levels of exposure, whereas a relatively small study may be able to detect the effect of heavy or sustained exposure to a toxic substance. In this way, a study’s precision or statistical power is also linked to the extent of the exposure and the accuracy of its measurement. Inaccurate assessment of exposure can obscure the existence of such a trend and thus make it less likely that a true risk will be identified.”<sup>13</sup>

Research programs, such as the federal program for Gulf War illnesses, are designed to lead to information and treatments in a timely and efficient manner. In the conventional model of epidemiological research, a research program to investigate a disease outbreak follows a study cycle. (See fig. I.2 for an illustration of this cycle.)<sup>14</sup> First, descriptive studies are conducted to gather basic information about patterns of illness, the natural environment, and exposures of interest (step one). Once enough information is gathered, researchers create hypotheses to explain the patterns that they see in these descriptive data (step two). Analytic studies are then conducted to test the hypotheses (step three). The results of these analytic studies are evaluated (step four). They may suggest a need to gather additional descriptive data (step one), or they may yield new or refined hypotheses (step two) to be tested in further analytic studies (step three). The cycle continues until the disease is adequately understood to permit the development of treatments. Applying this cycle is a useful way of organizing a research program when valid descriptive information can be acquired about exposures and dose/response relationships. However, when this information is not available, retaining this model, that is conducting descriptive studies that lead to hypotheses that are then tested, may not be timely or effective.

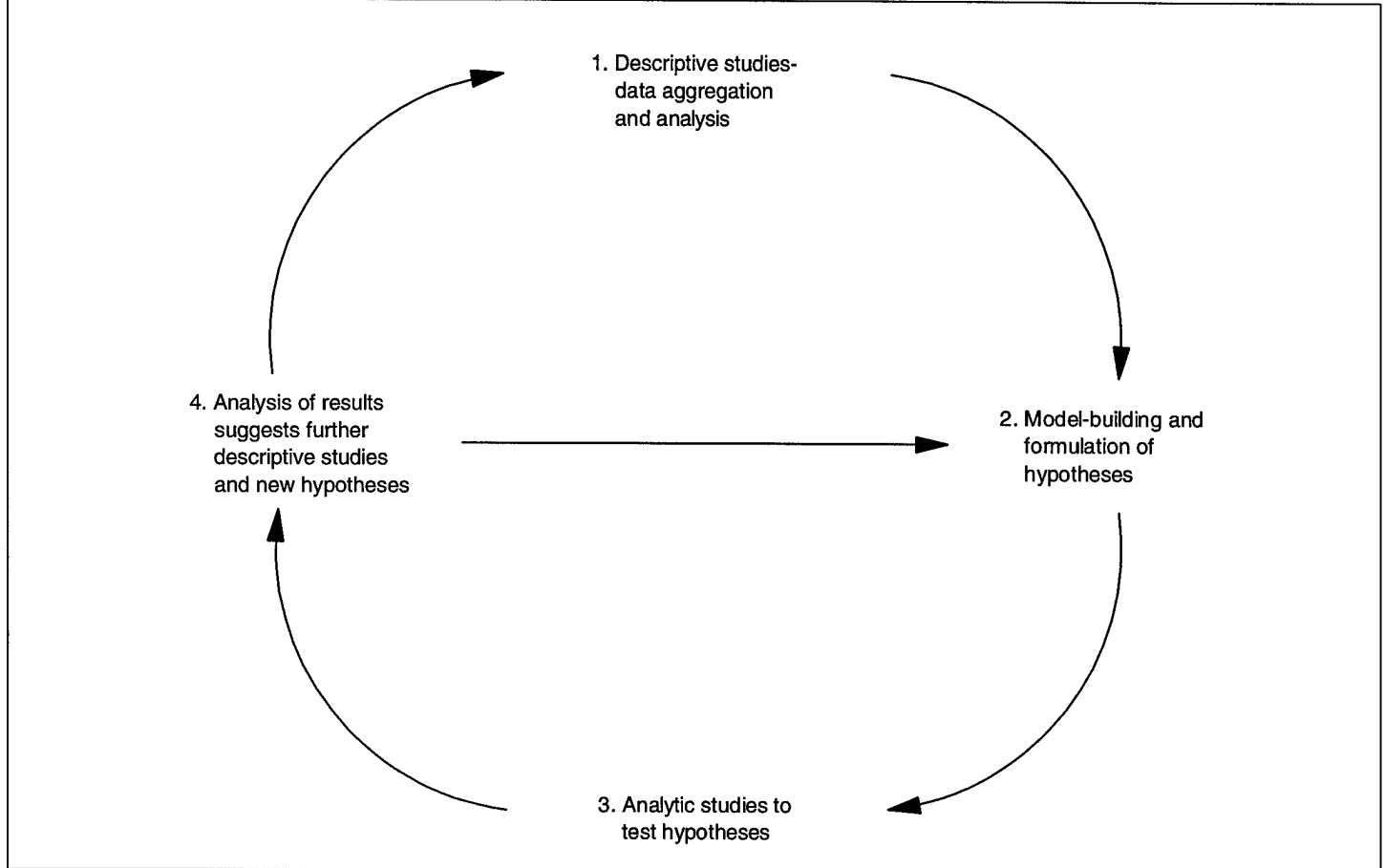
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<sup>13</sup>Veterans and Agent Orange: Update 1996 (Washington, D.C.: Institute of Medicine, 1996), pp. 99-100.

<sup>14</sup>This research model is shared by other scientific fields that also develop hypotheses and then test them through field or laboratory research.

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Figure I.2: Epidemiologic Study Cycles



Source: Mausner and Bahn, *Epidemiology—An Introductory Text*, p. 155.

# No Systematic Approach for Monitoring Veterans' Treatment After Initial Examination

Most veterans with symptoms who were evaluated in the VA and DOD health programs received a diagnosis (78 percent and 80 percent, respectively), while at least 20 percent have symptoms or signs that elude diagnosis. However, an analysis of 222 VA registrants in Portland, Oregon, showed that only 19 percent had symptoms that were fully explained by the coded registry diagnoses. This suggests that undiagnosed signs and symptoms may be more common than is apparent from initial analyses of registry data.

The most commonly reported symptoms in VA and DOD registries include fatigue, muscle and joint pain, gastrointestinal complaints, headache, skin rashes, depression, neurologic and neurocognitive impairments, memory loss, shortness of breath, and sleep disturbance. It is noteworthy that veterans participate in the registry programs even though (1) participation in the programs is voluntary and some members of the active duty service may perceive it as career-limiting; (2) the health registry programs provide only diagnostic services and treatment incidental to diagnosis (for example, removal of malignancies found during a diagnostic biopsy); and (3) the examination can be lengthy.

## No Mechanisms Exist to Monitor Veterans' Quality of Care

Officials of both DOD and VA have testified that whatever uncertainties may exist about the cause of veterans' illnesses, the veterans are at least receiving appropriate and effective symptomatic treatment.<sup>15</sup> In the case of veterans with no clear diagnosis, treatment is based on symptoms, and veterans with multiple diagnoses may see multiple types of providers. However, these agencies had no mechanisms for monitoring the quality of these veterans' care or their clinical progress after their initial examination, nor did they describe plans to establish such mechanisms.<sup>16</sup> VA delegates monitoring responsibilities to local veterans hospitals, which may monitor the quality of a subsample of services.<sup>17</sup>

<sup>15</sup>Testimony before the House Government Reform and Oversight Committee's Subcommittee on Human Resources and Intergovernmental Relations by VA's Chief Public Health and Environmental Hazards Officer, December 11, 1996, and a written statement submitted by Dr. Stephen C. Joseph, Assistant Secretary of Defense for Health Affairs, to a September 25, 1996, joint hearing of the Senate Select Intelligence and Veterans' Affairs Committees.

<sup>16</sup>Since November 1996, DOD has been working with independent contractors to determine appropriate health outcomes and other metrics that would characterize the current health status of those participating in the CCEP. In addition, a 5-year follow-up policy has been developed for the small number of soldiers suspected of being exposed to depleted uranium particles.

<sup>17</sup>The term "quality assurance" is used to describe prospective processes or requirements—such as licensure, inspections, or training—generally intended to promote a certain level of performance based on criteria that might be the subject of a quality measurement program (that is, indicators of the achievement of program goals or the capacity to achieve such goals).

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VA officials involved in administering PGHREP told us that they regarded monitoring the clinical progress of registry participants as a separate research project, and DOD's CCEP manager made similar comments. Instead, the two agencies have relied on such quality assurance mechanisms as standards for physician qualification and process measurements, although these do not necessarily ensure a given level of effectiveness for the care provided.<sup>18</sup>

Although VA's Central Office samples a subset of all veterans having contact with VA hospitals to determine their satisfaction with VA health care, VA officials told us that this sample is not currently large enough to provide information specific to veterans of the Gulf War. Similarly, local facilities may conduct studies of their success with a particular medical treatment (e.g., a coronary bypass), but these are unlikely to provide specific information on Gulf War veterans.<sup>19</sup>

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**Efforts to Ensure  
Quality and Measure  
Satisfaction With  
Initial Examination  
Are Not Adequate**

Both VA and DOD have applied some traditional quality assurance and measurement strategies to the initial examination of Gulf War veterans.<sup>20</sup> In response to a recommendation of the IOM, DOD has asked for feedback from CCEP participants; however, we have found some problems with DOD's approach to analyzing Gulf War veterans' responses to questionnaires relating to their satisfaction with CCEP evaluations. Specifically,

(1) Gulf War veterans' responses were not compared to responses from other groups of patients seeking diagnosis and treatment.

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<sup>18</sup>See Long-Term Care: Status of Quality Assurance and Measurement in Home and Community-Based Services (GAO/PEMD-94-19, Mar. 1994).

<sup>19</sup>For previous GAO reviews of performance monitoring and outcomes measurement in VA and DOD health care programs, see Defense Health Care: New Managed Care Plan Progressing, but Cost and Performance Issues Remain (GAO/HEHS-96-128); VA Health Care: Trends in Malpractice Claims Can Aid in Addressing Quality of Care Problems (GAO/HEHS-96-24); VA Health Care: Physician Peer Review Identifies Quality of Care Problems, but Actions to Address Them Are Limited (GAO/HEHS-95-121); Veterans' Health Care: Veterans' Perceptions of VA Services and VA's Role in Health Care Reform (GAO/HEHS-95-14); VA Health Care for Women: In Need of Continued VA Attention (GAO/HEHS-94-114); and VA Health Care: VA Medical Centers Need to Improve Monitoring of High-Risk Patients (GAO/HRD-94-27).

<sup>20</sup>DOD identified the following quality assurance measures that are in place for all DOD eligible individuals: The National Quality Management Program, Clinical Quality Management Program for the Military Health Service System. The National Quality Management Program comprises the following seven components: Medical Readiness, Accreditation of Healthcare Organizations, Licensure, Credentials and clinical Privileges, National Practitioner Data Bank, Utilization Management Oversight, and Special Studies.

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(2) DOD combined into a single category the "no opinion" and missing responses.

(3) It is unclear to what extent responses were included from patients who voluntarily declined participation in the program or were placed in an "administrative declination" category for "failure to become actively involved in the CCEP program."

In addition, no information is available on the extent to which active duty veterans have sought evaluations outside the CCEP program, which could be an indicator of patient dissatisfaction. VA plans to initiate a satisfaction measure for its PGHREP by incorporating a feedback postcard in the examination process. However, this plan has been under development for months, and VA officials told us it remained so as of March 24, 1997.

Both VA and DOD have applied some quality measurement to their registry examination processes. A VA directive requires VA medical centers to use the PGHREP Quality Management/Self-Assessment Monitor to review at least a 10-percent sample of all Persian Gulf registry physical examinations conducted from January 1, 1996, through September 30, 1996. The results of this process were submitted to VA's Environmental Agents Service and summarized for 167 of the VA's 173 medical centers. They showed a fairly high self-reported compliance with various aspects of the examination among reporting facilities. Although the results of this self-assessment process suggested that the overwhelming majority of veterans who were symptomatic at the time of the examination had a follow-up examination scheduled, 20 percent were not assigned to a primary care team, and 17 percent of their records lacked evidence of a follow-up letter containing examination results and recommendations.

Similarly, DOD tracks the aging of requests for CCEP examinations and provides feedback to its regional facilities on examinations that are overdue or reports that remain incomplete. DOD does not consider an examination complete until certain fields in the examination report have been filled in and submitted. Through supervisory personnel at 13 regional treatment centers, DOD also conducts some oversight of examination activities at its 148 CCEP administration sites.

# Federal Strategy to Research Gulf War Illnesses Lacks a Coherent Approach

The approach to collecting data on Persian Gulf veterans and the factors that might have caused their health problems has not been proactive, and articulation of a research agenda came years after the war. The subsequent research, which is largely epidemiological and still ongoing, has pursued some hypotheses more aggressively than others and faces formidable methodological problems.

## Goals of the Epidemiological Research

President Clinton established PGVCB on January 21, 1994, to coordinate federal efforts to address health concerns raised by veterans of the Persian Gulf War. Various federal agencies had previously independently addressed these concerns. The Research Working Group (RWG) of the PGVCB has primary responsibility for managing research into Gulf War illnesses. In August 1995, PGVCB identified three broad goals for research on veterans' illnesses: (1) determine the nature and prevalence of symptoms, illnesses, and unexplained conditions among Persian Gulf veterans; (2) identify possible causes for any illnesses found among Persian Gulf veterans; and (3) identify diagnostic tools, treatment methods, and prevention strategies for illnesses found among Persian Gulf veterans. These are generally accepted goals for the epidemiologic study of poorly understood conditions.

To support these research goals, PGVCB identified 21 more specific research objectives. (See table III.1.)

**Table III.1: Research Objectives Identified by PGVCB**

Number	Objective
1	What is the prevalence of symptoms/illnesses in the Gulf War veterans' population? How does this prevalence compare to that in an appropriate control group?
2	What was the overall exposure of troops to leishmania tropica?
3	What were the exposure concentrations to various petroleum products and their combustion products in typical usage during the Gulf War?
4	What was the extent of exposure to specific occupational/environmental hazards known to be common in the Gulf War veterans' experience? Was this exposure different from that of an appropriate control group?
5 <sup>a</sup>	What were the potential exposures of troops to organophosphate nerve agents and/or sulfur mustard as a result of allied bombing at Muhammadiyat and Al Muthanna or the demolition of a weapons bunker at Khamisiyah?
6 <sup>a</sup>	What was the extent of exposure to chemical agents, other than at Khamisiyah in the Gulf War as a function of space and time?
7	What was the prevalence of pyridostigmine bromide use among Gulf War troops?

(continued)

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<b>Number</b>	<b>Objective</b>
8	What was the prevalence of various psychophysiological stressors among Gulf War veterans? Is the prevalence different from that of an appropriate comparison population?
9	Are Gulf War veterans more likely than an appropriate comparison group to experience nonspecific symptoms and symptom-complexes?
10	Do Gulf War veterans have a greater prevalence of altered immune function or host defense when compared with an appropriate control group?
11	Is there a greater prevalence of birth defects in the offspring of Gulf War veterans than in an appropriate control population?
12	Have Gulf War veterans experienced lower reproductive success than an appropriate control population?
13	Is the prevalence of sexual dysfunction greater among Gulf War veterans than among an appropriate comparison population?
14	Do Gulf War veterans report more pulmonary symptoms or diagnoses than persons in an appropriate control population?
15	Do Gulf War veterans have a smaller baseline lung function in comparison to an appropriate control group? Do Gulf War veterans have a greater degree of nonspecific airway reactivity in comparison to an appropriate control group?
16	Is there a greater prevalence of organic neuropsychological and neurological deficits in Gulf War veterans compared to appropriate control populations?
17	Can short-term, low-level exposures to pyridostigmine bromide, the insect repellent DEET, and the insecticide permethrin, alone or in combination, cause short-term and/or long-term neurological effects?
18	Do Gulf War veterans have a significantly higher prevalence of psychological symptoms and/or diagnoses than do members of an appropriate control group?
19	What is the prevalence of leishmaniasis and other infectious diseases in the Gulf War veteran population?
20	Do Gulf War veterans have a greater risk of developing cancers of any type when compared with an appropriate control population?
21	Are Gulf War veterans experiencing a mortality rate that is greater than that of an appropriate control population? Are specific causes of death related to service in the Persian Gulf?

<sup>a</sup>Objective was added in 1996, following DOD's announcement of potential exposures to chemical warfare agents in postwar operations at three sites.

**In connection with these research objectives, 91 specific studies were identified in the most recent annual report to Congress on federally**



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sponsored research on Gulf War veterans' illnesses.<sup>21</sup> (See table III.2.) According to figures reported by the agencies, through fiscal year 1996, DOD expended \$19.9 million on these research efforts, VA spent \$11.6 million, and HHS attributes expenditures of \$5.5 million to the four projects it has pursued. In all, these agencies spent about \$37 million for research through fiscal year 1996. Additional amounts have been made available for ongoing and future projects.

**Table III.2: PGVCB Research Projects**

Project no.	Title	Status	Location	Start date	Completion date	Expenditures through FY96 <sup>a</sup>
DoD-1A	Epidemiologic Studies of Morbidity Among Gulf War Veterans: A Search for Etiologic Agents and Risk Factors	Ongoing	NHRC	6/1/94	10/1/96	\$3,985,000
DoD-1B	A Search for Etiologic Agents and Risk Factors: Study 2	Complete	NHRC	7/1/94	10/1/96	See DoD-1A
DoD-1C	A comparative study of pregnancy outcomes	Complete	NHRC	9/1/94	6/1/96	See DoD-1A
DoD-1D	Infertility and Miscarriage in Gulf War Veterans	Ongoing	NHRC	11/1/94	9/1/97	See DoD-1A
DoD-1E	Seabee Health Study	Ongoing	NHRC	1/1/96	10/1/2011	See DoD-1A
DoD-1F	A Comparison of Nonfederal Hosp. Experience Among Veterans in California ...	Ongoing	NHRC	6/1/95	6/1/97	See DoD-1A
DoD-1G	Epidemiologic Studies of Morbidity —Study 7: Prevalence of Congenital Anomalies Among Children of Persian Gulf War Veterans	Ongoing	NHRC	6/1/95	6/1/97	See DoD-1A
DoD-2	Physiological and Neurobehavioral Effects in Rodents from Exposure to PB, Fuels, and DEET	Ongoing	USAMRD (Wright-Patterson)	7/1/94	10/1/97	\$90,000
DoD-4	The General Well-Being of Gulf War Era Service Personnel from the States of PA and HI	Complete	WRAIR	9/1/92	5/20/94	\$1,200,000
DoD-6A	Combat Stress Pharmacotherapy	Ongoing	WRAIR	10/1/88	9/30/99	\$30,000
DoD-6B	Combat Stress Diagnosis: PTSD Prevention	Ongoing	WRAIR	10/1/87	9/30/98	0
DoD-7A	Health Risk Assessment of Embedded Depleted Uranium	Ongoing	AFFRI	12/1/94	1/30/98	\$703,000
DoD-7B	Carcinogenicity of Depleted Uranium Fragments	Ongoing	ITRI	1/26/95	10/30/98	\$549,000
DoD-8A	Serologic Diagnosis of Viscerotropic Leishmaniasis	Complete	WRAIR	10/1/93	9/1/96	\$10,000
DoD-8B	Development of Leishmania Skin Test Antigen	Ongoing	WRAIR	10/1/93	1/31/2000	\$421,000

(continued)

<sup>21</sup>The Research Working Group of the Persian Gulf Veterans Coordinating Board, *Annual Report to Congress: Federally Sponsored Research on Gulf War veterans' Illnesses* (Washington, D.C.: Department of Veterans Affairs, Apr. 1997). Also see PGVCB, *A Working Plan for Research on Persian Gulf Veterans' Illnesses* (Washington, D.C.: VA, Nov. 1996).

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<b>Project no.</b>	<b>Title</b>	<b>Status</b>	<b>Location</b>	<b>Start date</b>	<b>Completion date</b>	<b>Expenditures through FY96*</b>
DoD-9	Identification of the Genetic Factors Which Control Tropism in Leishmania	Ongoing	USAMRU-Brazil	7/1/94	7/1/98	\$150,000
DoD-10	Pyridostigmine Synergistic Toxicity Study	Complete	CHPPM	11/1/94	3/1/94	\$44,000
DoD-11	Male/Female Differential Tolerances to Pyridostigmine Bromide	Ongoing	South Florida Drug Research	10/1/94	2/1/97	\$908,000
DoD-12	Forward Deployable Diagnostics for Infectious Diseases	Ongoing	MRMC	10/1/93	9/30/2001	\$1,546,000
DoD-13	Effects of Persian Gulf War Service on Military Working Dogs	Ongoing	AFIP	4/1/94	12/1/98	\$200,000
DoD-14	Risk Factors Among U.S. Soldiers for Enrolling on the Department of Veterans Affairs Gulf War Registry	Ongoing	WRAIR	10/1/93	9/1/96	\$70,000
DoD-15	Comparative Mortality Among US Military Personnel Worldwide During Operations Desert Shield and Desert Storm	Complete	WRAIR	5/1/94	1/1/95	\$20,000
DoD-16	Kuwait Oil Fire Health Risk Assessment	Complete	CHPPM	5/5/91	2/18/94	\$1,805,000
DoD-17	Retrospective Studies Involving Military Use of PB as a Pretreatment for Nerve Agent Poisoning	Complete	CHPPM	1/1/91	5/21/92	\$21,000
DoD-18	Kuwait Oil Fires Troop Exposure Assessment Model (TEAM)	Complete	CHPPM	5/31/93	12/31/96	\$1,500,000
DoD-19	Persian Gulf Veterans Health Tracking System	Ongoing	CHPPM	4/1/96	12/31/97	\$25,000
DoD-20	A Statistical Study Correlating the Reported Cases of Gulf War Syndrome to Battlefield Locations of Afflicted US Army Personnel During the Iraq-Kuwait War	Complete	U.S. Army Research Lab.	1/1/94	7/1/95	\$50,000
DoD-21	Study of Variability in Pyridostigmine Inhibition of Blood Cholinesterases in Healthy Adults ...	Ongoing	WRAIR and WRAMC	7/11/95	6/30/97	\$138,000
DoD-22	Chronic Organophosphorus Exposure and Cognition	Ongoing	University of GA	4/15/95	5/14/98	\$187,000
DoD-23	Acute and Long-Term Impact of Deployment to Southwest Asia on the Physical and Mental Health of Soldiers and their Families	Ongoing	WRAIR	10/1/93	9/1/98	\$326,000
DoD-30	Epidemiological Studies Persian Gulf War Illnesses, PG Women's Health Linkage Study	Ongoing	Klemm Analysis, DC	6/1/96	1/31/99	\$779,000
DoD-31	Dysregulation of the Stress Responses in the Persian Gulf Syndrome	Ongoing	Georgetown Univ., DC	5/6/96	6/6/99	\$162,000
DoD-32	Neuropsychological Functioning in Persian Gulf Era Veterans	Ongoing	VAMC Boston	5/1/96	5/1/99	\$353,000
DoD-33	Effects of Pyridostigmine in Flinders Line Rats Differing in Cholinergic Sensitivity	Ongoing	Chapel Hill	7/1/96	6/30/98	\$44,000
DoD-34	Characterization of Emissions from Heaters Burning Leaded Diesel Fuel in Unvented Tents	Ongoing	Lovelace Biomedical Albuquerque, NM	6/7/96	7/6/98	\$36,000

(continued)

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<b>Project no.</b>	<b>Title</b>	<b>Status</b>	<b>Location</b>	<b>Start date</b>	<b>Completion date</b>	<b>Expenditures through FY96<sup>a</sup></b>
DoD-35	Feasibility of Investigating whether there is a Relationship Between Birth Defects and Service in the Gulf War	Ongoing	March of Dimes, Sacramento, CA	6/1/96	6/30/98	\$110,000
DoD-36	Fatigue in Persian Gulf Syndrome-Physiologic Mechanisms	Ongoing	Dallas	6/15/96	7/14/98	\$138,000
DoD-37	Neurobehavioral and Immunological Toxicity of Pyridostigmine, Permethrin, and DEET in Male and Female Rats	Ongoing	Gainesville	5/1/96	6/1/99	\$132,000
DoD-38	Diagnostic Antigens of Leishmania tropica	Ongoing	Infectious Disease Research Inst., Seattle, WA	6/1/96	5/31/98	\$612,000
DoD-39	A Controlled Epidemiological and Clinical Study into the Effects of Gulf War Service on ... UK Armed Forces	Ongoing	UK	6/1/96	6/30/99	\$865,000
DoD-40	Psychological and Neurobiological Consequences of the Gulf War Experiences	Ongoing	VAMC West Haven	6/7/96	7/6/99	\$90,000
DoD-41	Evaluation of Muscle Function in Persian Gulf Veterans	Ongoing	Philadelphia	6/15/96	11/14/99	\$906,000
DoD-42	The Symptomatic Persian Gulf Veterans Protocol: An Analysis of Risk Factors with an Immunologic and Neuropsychiatric Assessment	Ongoing	VAMC Birmingham	10/31/96	2000	\$700,000
DoD-44	Investigation of Seminal Plasma Hypersensitivity Reactions	Ongoing	Univ. Cincinnati	11/1/96	10/1/99	\$634,000
DoD-45	Physical and Emotional Health of Gulf War Veterans Women	Ongoing	Ann Arbor, MI	9/1/96	8/31/99	\$100,000
DoD-46	Exploratory Data Analysis with the CCEP Database	Ongoing	NPGS - Missouri	10/1/95	9/1/97	\$60,000
DoD-47	Study of Mycoplasmal Infections in Gulf War Veterans	Ongoing	WRAMC	10/10/95	8/30/97	\$112,000
DoD-48	Assessment of Genomic Instability via Chromosome 7 Inversion Frequency in a Gulf-War Syndrome Cohort vs. Selected Control Groups	Ongoing	AFIP	10/10/95	5/31/97	\$74,000
DoD-49	Diagnosis and Dosimetry of Exposure to Sulfur Mustard	Ongoing	Netherlands	10/1/96	2/28/2000	Not available
DoD-50	Toxicokinetics of VX	Ongoing	Netherlands	10/15/96	4/30/98	Not available
DoD-51	Transgenic Engineering of Cholinesterases	Ongoing	Israel	10/1/96	2/28/2000	Not available
HHS-1	Health Assessment of Persian Gulf War Veterans from Iowa	Ongoing	CDC	12/1/94	1/31/98	\$4,772,000
HHS-2	Disease Cluster in a Pennsylvania Air National Guard Unit, EPI-AID 95-18	Ongoing	CDC	12/1/94	3/31/95	\$750,000

(continued)

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<b>Project no.</b>	<b>Title</b>	<b>Status</b>	<b>Location</b>	<b>Start date</b>	<b>Completion date</b>	<b>Expenditures through FY96<sup>a</sup></b>
HHS-3	Biomarkers of Susceptibility and Polycyclic Aromatic Hydrocarbon Exposure in Urine and Blood Cell DNA from US Army Soldiers Exposed to Kuwaiti Oil Well Fires	Ongoing	NIH/NCI/DCE /LCTP/IVP	1/1/92	1/31/97	<sup>b</sup>
HHS-4	Suspected Increase of Birth Defects and Health Problems Among Children Born to Persian Gulf War Veterans in Mississippi	Complete	CDC	5/1/94	2/1/96	\$15,981 <sup>c</sup>
VA-1	Mortality Follow-up Study of Persian Gulf Veterans	Complete	VACO	7/1/94	7/31/96	\$150,000
VA-2	National Health Survey of Persian Gulf Veterans	Ongoing	VACO	7/1/94	6/30/98	\$2,716,000
VA-3	Use of Roster of Veterans Who Served in Persian Gulf Area	Ongoing	VACO	7/1/94	7/31/96	0
VA-4A	Evaluation of Cognitive Functioning of Persian Gulf Veterans	Ongoing	VAMC Boston	10/1/94	9/30/99	\$2,572,500
VA-4B	Evaluation of Neurological Functioning of Persian Gulf Veterans	Ongoing	VAMC Boston	10/1/94	9/30/99	See VA-4A
VA-4C	Gulf War and Vietnam Veterans Cancer Incidence Surveillance	Ongoing	VAMC Boston	10/1/94	9/30/99	See VA-4A
VA-4D	Evaluation of Respiratory Dysfunction Among Gulf War Veterans	Ongoing	VAMC Boston	10/1/94	9/30/96	See VA-4A
VA-4E	The Aromatic Hydrocarbon Receptor as a Biomarker of Susceptibility	Ongoing	VAMC Boston	10/1/94	9/30/99	See VA-4A
VA-4F	Validity of Computerized Tests	Ongoing	VAMC Boston	10/1/94	9/30/99	See VA-4A
VA-5A	Health and Exposure Survey of Persian Gulf Veterans	Ongoing	VAMC E. Orange	10/1/94	9/30/96	\$2,572,500
VA-5B	Physiological and Psychological Assessments of Persian Gulf Veterans	Ongoing	VAMC E. Orange	10/1/94	3/1/97	See VA-5A
VA-5C	Effects of Exertion and Chemical Stress on Persian Gulf Veterans	Ongoing	VAMC E. Orange	4/1/97	9/30/99	See VA-5A
VA-5D	Effects of Genetics and Stress on Responses to Environmental Toxins	Ongoing	VAMC E. Orange	10/1/94	9/30/97	See VA-5A
VA-6	Portland Environmental Hazards Research Center: Environmental, Veterans Health and the Gulf War Syndrome	Ongoing	VAMC Portland	10/1/94	9/30/99	\$2,572,500
VA-6A	Psychosocial, Neuropsychological and Neurobehavioral Assessment	Ongoing	VAMC Portland	10/1/94	9/30/99	See VA-6
VA-6B	Clinical and Neuroendocrine Aspects of Fibromyalgia (Project II)	Ongoing	VAMC Portland	10/1/94	9/30/99	See VA-6
VA-6C	Neurotoxicity of Environmental Pollutants and Warfare Agents (Project III)	Ongoing	VAMC Portland	10/1/94	9/30/99	See VA-6
VA-6D	DNA Damage from Chemical Agents and its Repair (Project IV)	Ongoing	VAMC Portland	10/1/94	9/30/99	See VA-6
VA-7	Desert Storm Reunion Survey	Complete	VAMC Boston	4/1/91	9/30/95	\$122,500

(continued)

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<b>Project no.</b>	<b>Title</b>	<b>Status</b>	<b>Location</b>	<b>Start date</b>	<b>Completion date</b>	<b>Expenditures through FY96<sup>a</sup></b>
VA-8	Psychological Test Data of Gulf War Veterans over Time	Ongoing	VAMC Mountain Home	7/9/91	9/30/97	Not available
VA-9	Evaluation of Cognitive Functioning in Persian Gulf War Veterans Reporting War-related Health Problems	Complete	VAMC New Orleans	4/1/94	9/30/95	\$49,000
VA-10	Memory and Attention in PTSD	Ongoing	VAMC New Orleans	2/1/94	9/30/98	\$156,065
VA-11	Neuropsychological Functioning in Veterans	Complete	VAMC New Orleans	2/1/92	3/1/95	Not available
VA-12	Psychological Assessment of Operation Desert Storm Returnees	Ongoing	VAMC New Orleans	8/1/91	9/1/97	Not available
VA-13	Neurobehavioral Aspects of Persian Gulf Experiences: A Pilot Study	Complete	VAMC Pittsburgh	4/1/94	3/31/95	\$122,500
VA-15	Vaccine-Mediated Immunity Against Leishmaniasis	Ongoing	VAMC Cleveland	1/1/93	9/30/99	\$315,070
VA-16	Protective Immunity in Experimental Visceral Leishmaniasis	Ongoing	VAMC San Antonio	10/1/94	9/30/97	\$296,205
VA-17	Immunological Evaluation of Persian Gulf Veterans	Complete	VAMC Birmingham	4/1/94	5/1/95	Not available
VA-18	Chronic Gastrointestinal Illness in Persian Gulf Veterans	Ongoing	VAMC Boston	10/1/94	10/1/96	Not available
VA-20	Psychological Adjustment in Operation Desert Shield/Storm Veterans	Complete	VAMC Gainesville	7/1/91	7/1/93	Not available
VA-21	A Comparison of PTSD Symptomatology among Three Army Medical Units Involved in ODS	Complete	VAMC Phoenix	1/8/92	12/3/94	Not available
VA-30	Female Gender and Other Potential Predictors of Functional Health Status Among Persian Gulf War Veterans	Ongoing	VAMC Boston	9/11/95	3/19/98	Not available
VA-36	Stress Symptoms and their Causal Attribution in Desert Storm Veterans	Ongoing	VAMC Clarksburg	12/1/95	12/31/96	Not available
VA-40	Musculoskeletal Symptoms in Gulf War Syndrome	Ongoing	VAMC Long Beach	1/1/94	1999	Not available
VA-46	Diarrhea in Persian Gulf Veterans: An Irritable Bowel-Like Disorder	Ongoing	VAMC Gainesville	11/1/95	1996	Not available
VA-47	Retrospective Validation of Mustard Gas Exposure	Ongoing	VAMC Louisville	1/1/97	2000	Not available
						<b>\$37,067,821</b>

(Table notes on next page)

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<sup>a</sup>Information on funding was unavailable for some VA intramural projects because these projects were budgeted from medical center overhead. Additional funds may have been obligated for ongoing projects in fiscal year 1997 and later years.

<sup>b</sup>HHS conducted testing on blood samples from persons exposed to the Kuwait oil well fires to assess evidence of exposure to volatile organic compounds. The cost incurred for this work was \$33,000.

<sup>c</sup>Federal costs only.

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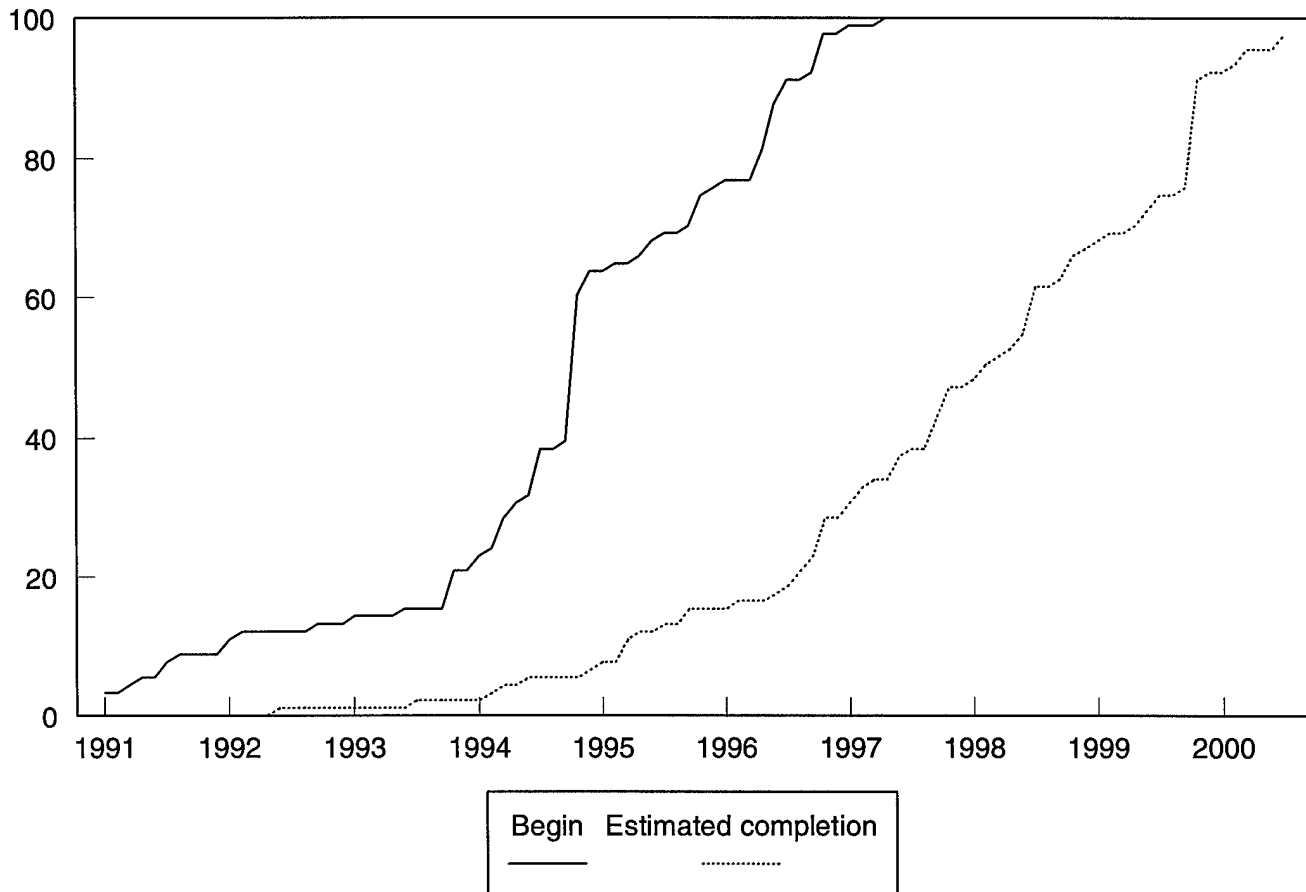
**Federal Research Was  
Delayed and Lacked a  
Proactive Approach**

The vast majority of federal research was initiated during or after 1994, and relatively few of these studies have been completed. Seventy-two projects (79 percent) were ongoing when we reviewed them in early 1997. Figure III.1, which shows the proportion of completed studies, is based on the rate of progress toward completion of projects based on actual and projected completion dates provided in the most recent research working plan. In some instances, the projected completion dates have not been met. Therefore, figure III.1 slightly overstates the number of projects actually completed. In fact, 28 studies have estimated completion dates prior to 1997, yet only 19 have been flagged as complete in the most recent (April 1997) report to Congress.

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Figure III.1: Cumulative Percentages of 91 Federally Funded Studies to Be Completed as a Function of Time

Percent of 91 studies



Note: An additional two studies are slated to continue beyond the year 2000.

Source: GAO analysis of information published by the PGVCB.

Many federal research efforts were started in association with legislation enacted by Congress. For example, legislation enacted in December 1991 required DOD to establish a registry of troop members who were exposed to fumes from oil well fires and to report annually on its studies of the health effects of such exposure. Legislation enacted in late 1993

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authorized DOD to make grants for studies on the effects of veterans' exposure to low levels of hazardous chemicals, including chemical warfare agents, and on the effects of exposure to depleted uranium. In 1994, Congress required DOD, in consultation with the VA and HHS, to conduct studies and administer grants for studies to determine the nature and causes of Gulf War illness, including, among others, studies to determine the effects of exposure to pyridostigmine bromide. In 1996, Congress directed DOD to provide for research into the possible exposure of troops to chemical warfare agents or other hazardous materials and the use by DOD of combinations of various vaccines and investigational new drugs.

As noted by external reviewers, since federal research goals and objectives were not identified until 1995, after most research activities had been initiated, they appear to reflect a rationalization of ongoing activity rather than a research management strategy. In March 1995, the Department of Veterans Affairs issued a report to Congress, entitled Federal Activities Related to the Health of Persian Gulf Veterans, that identified most of the projects now covered by the PGVCB's research agenda but noted that "this is a list of activities and is not intended to be construed as a comprehensive research strategy." Five months later, PGVCB issued A Working Plan for Research on Persian Gulf Veterans' Illnesses, which linked the previously identified projects to 19 specific research objectives. VA officials acknowledged that the research strategy was articulated in response to criticism from the IOM, which had said that "VA and DOD should determine the specific research questions that need to be answered." Table III.3 documents other events coincident with changes in research activity.



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**Table III.3: Events Coincident With Changes in PGVCB Research Agenda**

	1991	1992	1993	1994	1995	1996
Events and reports	<b>Operation Desert Storm</b> (winter)	Reports of "unexpected signs and symptoms" from the 123rd Army Reserve Unit in Indiana. (January)	A staff report to the <b>Senate Banking Committee</b> states that "there is substantial evidence supporting claims that U.S. servicemen and women were exposed to low level chemical warfare agents and possibly biological toxins from a variety of possible sources. This exposure may account for many of the Gulf War illness symptoms."	The <b>Defense Science Board</b> report states that illnesses were not due to exposure to chemical weapons. (June)  <b>NIH Technology Assessment Workshop</b> finds that (1) a collaborative government-supported program had not been established and (2) the absence of well-designed studies had hampered the development of an appropriate case definition. (April)	<b>IOM interim report</b> criticizes agencies for lack of coordination.	<b>DOD acknowledges chemical weapon release at Khamisiyah.</b>  Presidential Advisory Committee report finds that "The government's current research portfolio on Gulf War veterans' illnesses is appropriately weighted toward epidemiologic studies and studies on stress-related disorders."

(continued)

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	<b>1991</b>	<b>1992</b>	<b>1993</b>	<b>1994</b>	<b>1995</b>	<b>1996</b>
Research program	Six new studies started  Four on stress and one each on oil well fires and PB	Four new studies started  Three on stress and one on methods	Seven new studies started  Four on infectious diseases, one each on stress, oil fires, and methods	39 new studies started (including 14 at the environmental health centers)  Shift to include a greater range of symptoms and exposures  VA establishes three environmental hazards research centers. (July)	Eleven new studies started  President announces formation of Presidential Advisory Committee (March)  DOD issues a "Broad Agency Announcement" for research in PB, epidemiology and clinical research as mandated by Congress in PL 103-337. \$5 million allocated. There were more than 100 responses. (June)	20 new studies started  \$2.5 million allocated by VA to three new projects examining the health effects of chemical weapons.  DOD launches a \$15 million research program into the possible effects of low-level exposure to chemical agents using \$10 million made available by Congress and \$5 million committed by DOD. (September)  VA issues a request for proposals for a fourth Environmental Hazards Research Center for Reproductive Outcomes. (May)
Clinical care programs	VA develops the Persian Gulf Health Registry (April)			DOD starts the Comprehensive Clinical Evaluation Program (CCEP) (June)	DOD issues its report on the first 10,000 participants in CCEP (August)	DOD reports on the first 18,000 participants in CCEP (April)

Although research activity has recently been accelerated and broadened, opportunities have been missed to collect critical data that researchers cannot accurately reconstruct. Even efforts to measure the chemical content of the oil-fire smoke, begun only 3 months after the fires began burning, were initiated after most troops had left the affected areas and the climatological dynamics may have been different. Consequently, researchers were forced to use statistical models of the behavior of smoke plumes in order to infer the ground-level exposures experienced by the

large numbers of troops who had departed by the time they began collecting data. Even if such models accurately explain the behavior of the smoke plumes, they have not been validated as measures of individual exposure, and their accuracy for this purpose cannot be presumed. Similar and even more serious problems were caused in the measurement of other exposures by the failure to collect data promptly and maintain adequate records.<sup>22</sup>

The delay in starting research has also hindered accurate reporting of exposures by Gulf War veterans. Questionnaires are being distributed today (6 years after the war ended) requesting information from veterans on their exposure to certain agents during Operation Desert Storm. Regarding one study, the IOM concluded, "This is a well-designed and well-intended study, but it has started at least several years too late. Recall problems and the inability to obtain accurate information on those who died before the study started are major threats to its validity." (IOM, Final Report, 1996, p. 91)

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## Some Hypotheses Received Early Emphasis

Early federal research appeared to emphasize risks associated with psychological factors such as stress. To support this emphasis, DOD pointed out that the psychological state of mind can influence physical well-being. DOD also pointed to a recent argument that from the American Civil War onward (and perhaps even earlier), a small number of veterans have reacted to the stress of war by suffering symptoms similar to those reported by some Gulf War veterans.<sup>23</sup>

Of the 19 studies initiated before 1994, roughly half focused on exposure to stress or the potential for posttraumatic stress disorder (PTSD) among returning troops.<sup>24</sup> As late as December 1996, the Presidential Advisory Committee (PAC) on Gulf War Veterans' Illnesses noted that 25 studies centered on stress or PTSD. However, some early research reflected immediate postwar concerns about other issues, for example, the potential effects of the oil fires set by Iraqi troops departing Kuwait and an unusual form of parasitic infection that had been identified in a small number of patients at Walter Reed Army Medical Center (WRAMC).

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<sup>22</sup>See Defense Health Care: Medical Surveillance Has Improved Since the Gulf War, but Results in Bosnia Are Mixed (GAO/NSIAD-97-136, May 13, 1997) and Institute of Medicine, Final Report, p. 5.

<sup>23</sup>K. C. Hyams et al., "War Syndromes and Their Evaluation: From the U.S. Civil War to the Persian Gulf War," Annals of Internal Medicine, vol. 125 (1996), pp. 398-405.

<sup>24</sup>An additional 3 of the 19 studies did not provide information about veterans' illnesses but were instead building databases or methods to be used in later studies. Notably, according to the PGVCB, none of these 3 studies has yet been completed.

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## Some Hypotheses Were Not Initially Pursued

While research on exposure to stress received early emphasis, other hypotheses received scant support. In its Final Report, IOM discusses the evidence for a number of disease hypotheses, including multiple chemical sensitivity and organophosphate-induced delayed neuropathy (OPIDN). IOM found the evidence for none of the hypotheses to be highly compelling when it conducted the review, but it nevertheless highlighted the importance of exploring “all possible avenues to increase our knowledge of such illnesses and to reduce suffering and disability.” Nonetheless, aside from studies examining stress-related symptoms, relatively few studies have been supported to evaluate alternative disease hypotheses. For example, prior to October 1996, only one study focused on the health effects of potential exposure to chemical warfare agents.<sup>25</sup> While multiple studies of the role of stress in the veterans’ illnesses have been supported with federal research dollars, some other hypotheses have been pursued largely outside the federal research program.

Although veterans raised concerns about potential chemical exposures soon after the war, and DOD had acknowledged one soldier’s accidental exposure to a mustard agent in 1994, the federal research plan was not modified to include an investigation of concerns about such agents until 1996, when DOD acknowledged potential exposures to chemical agents at Khamisiyah, Iraq. The failure to fund such research cannot be traced to an absence of investigator-initiated submissions. According to DOD officials, three recently funded proposals on low-level chemical exposure had previously been denied funds.<sup>26</sup> (See DOD studies 49, 50, and 51 in table III.2)

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## Additional Hypotheses Were Pursued in the Private Sector

A substantial body of privately funded research suggests that low-level exposure to certain chemical warfare agents or chemically related compounds, such as certain pesticides, is associated with delayed or long-term health effects. Regarding delayed health effects of organophosphates, the chemical family used in many pesticides and chemical warfare agents, there is evidence from animal experiments, studies of accidental human exposures, and epidemiological studies of humans that low-level exposures to certain organophosphorus

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<sup>25</sup>This study of the impacts of sulfur mustard agent is a collaborative effort between the Portland Veterans Affairs Medical Center and the Oregon Health Sciences University. The principal investigator for the study pointed out that the possibility of chemical warfare exposure seemed plausible even in 1994 when he sought initial funding for this research.

<sup>26</sup>The three previously unfunded proposals address central nervous system targets for organophosphates, development of a DNA-based method for assessing mustard agent exposure, and work on the pharmacokinetics of the nerve agent VX.

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compounds, including sarin nerve agents to which some of our troops may have been exposed, can cause delayed, chronic neurotoxic effects.<sup>27</sup> This syndrome is characterized by clinical signs and symptoms manifested 4 to 21 days after exposure to organophosphate compounds. The symptoms of delayed neurotoxicity can take at least two forms: (1) a single large dose may cause nerve damage with paralysis and later spastic movement, or (2) repetitive low doses may damage the brain, causing impaired concentration and memory, depression, fatigue, and irritability. These delayed symptoms may be permanent.

As early as the 1950s, studies demonstrated that repeated oral and subcutaneous exposures to neurotoxic organophosphates produced delayed neurotoxic effects in rats and mice. In addition, German personnel who were exposed to nerve agents during World War II displayed signs and symptoms of neurological problems even 5 to 10 years after their last exposure. Long-term abnormal neurological and psychiatric symptoms as well as disturbed brain wave patterns have also been seen in workers exposed to sarin in sarin manufacturing plants.<sup>28</sup> The same abnormal brain wave disturbances were produced experimentally in primates by exposing them to low doses of sarin.<sup>29</sup>

Delayed, chronic neurotoxic effects were also seen in animal experiments after the administration of organophosphate.<sup>30</sup> These effects include difficulty in walking and paralysis. In recent experiments, animals given a low dosage of the nerve agent sarin for 10 days showed no signs of immediate illness but developed delayed chronic neurotoxicity after 2 weeks.<sup>31</sup>

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<sup>27</sup>Sarin has been used as a chemical warfare agent since World War II, most recently during the Iran-Iraq war, and by terrorists in Japan.

<sup>28</sup>F. H. Duffy et al., "Long-Term Effects of an Organophosphate Upon the Human Electroencephalogram," *Toxicology and Applied Pharmacology*, vol. 47 (1979), pp. 161-176, and F.R. Sidell, "Soman and Sarin: Clinical Manifestations and Treatment of Accidental Poisoning by Organophosphates," *Clinical Toxicology*, vol. 7 (1979), pp. 1-17.

<sup>29</sup>J. L. Burchfiel et al., "Persistent Effect of Sarin and Dieldrin Upon the Primate Electroencephalogram," *Toxicology and Applied Pharmacology*, vol. 35 (1976), pp. 365-379.

<sup>30</sup>M. B. Abou-Donia, "Organophosphorus Ester-induced Delayed Neurotoxicity," *Annual Review of Pharmacological Toxicology*, vol. 21 (1981), pp. 511-548, and M. K. Johnson, "The Target for Initiation of Delayed Neurotoxicity by Organophosphorus Esters: Biochemical Studies and Neurotoxicological Applications," *Review of Biochemistry and Toxicology*, vol. 4 (1982), pp. 141-212.

<sup>31</sup>K. Husain et al., "Assessing Delayed Neurotoxicity in Rodents after Nerve Gas Exposure," *Defence Science Journal*, vol. 44 (1994), pp. 161-164; K. Husain et al., "Delayed Neurotoxic Effect of Sarin in Mice After Repeated Inhalation Exposure," *Journal of Applied Toxicology*, vol. 13 (1993), pp. 143-145; and K. Husain et al., "A Comparative Study of Delayed Neurotoxicity in Hens Following Repeated Administration of Organophosphorus Compounds," *Indian Journal of Physiology and Pharmacology*, vol. 39 (1995), pp. 47-50.

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It has been suggested that the ill-defined symptoms experienced by Gulf War veterans may be due in part to OPIDN.<sup>32</sup> This hypothesis was tested in a privately supported epidemiological study of Gulf War veterans.<sup>33</sup> In addition to clarifying the patterns among veterans' symptoms by use of statistical factor analysis, this study demonstrated that vague symptoms of the ill veterans are associated with objective brain and nerve damage compatible with the known chronic effects of exposures to low levels of organophosphates.<sup>34</sup> It further linked the veterans' illnesses to exposure to combinations of chemicals, including nerve agents, pesticides in flea collars, N,N-diethyl-m-toluamide (DEET) in highly concentrated insect repellents, and pyridostigmine bromide tablets.

Toxicological research indicates that agents like pyridostigmine bromide, which Gulf War veterans took to protect themselves against the immediate, life-threatening effects of nerve agents, may alter the metabolism of organophosphates in ways that activate their delayed, chronic effects on the brain.<sup>35</sup> Moreover, exposure to combinations of organophosphates and related chemicals like pyridostigmine bromide or DEET has been shown in animal studies to be far more likely to cause morbidity and mortality than any of the chemicals acting alone.<sup>36</sup>

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<sup>32</sup>R. W. Haley et al., "Preliminary Findings of Studies on the Gulf War Syndrome," Presentations to the Intergovernmental Coordinating Board for the Gulf War Illness and the Staff of the Presidential Advisory Committee on Gulf War Veterans' Illnesses, September 16, 1995; R. W. Haley, "Organophosphate-Induced Delayed Neurotoxicity," Internal Medicine Grand Rounds, University of Texas Southwestern Medical Center, Dallas, Texas, October 10, 1996; and G. A. Jamal et al., "The Gulf War Syndrome: Is There Evidence of Dysfunction in the Nervous System?" Journal of Neurology, Neurosurgery and Psychiatry, vol. 60 (1996), pp. 449-451.

<sup>33</sup>This research, conducted at the University of Texas Southwestern Medical Center, has been supported in part by funding from the Perot Foundation.

<sup>34</sup>R. W. Haley et al., "Is There a Gulf War Syndrome? Searching for Syndromes by Factor Analysis of Symptoms," Journal of American Medical Association, vol. 277 (1997), pp. 215-222; R. W. Haley et al., "Evaluation of Neurologic Function in Gulf War Veterans: A Blinded Case-Control Study," Journal of American Medical Association, vol. 277 (1997), pp. 223-230; and R. W. Haley et al., "Self-reported Exposure to Neurotoxic Chemical Combinations in the Gulf War: A Cross-sectional Epidemiologic Study," Journal of American Medical Association, vol. 277 (1997), pp. 231-237.

<sup>35</sup>C. N. Pope and S. Padilla, "Potentiation of Organophosphorus Delayed Neurotoxicity," Journal of Toxicology and Environmental Health, vol. 31 (1990), pp. 261-273.

<sup>36</sup>M. B. Abou-Donia et al., "Increased Neurotoxicity Following Concurrent Exposure to Pyridostigmine Bromide, DEET, and Chlorpyrifos," Fundamentals of Applied Toxicology, vol. 34 (1996), pp. 201-222, and M. B. Abou-Donia et al., "Neurotoxicity Resulting From Coexposure to Pyridostigmine Bromide, DEET, and Permethrin," Journal of Toxicology and Environmental Health, vol. 48 (1996), pp. 35-56.

## Federal Research Emphasis

### Most Studies Use an Epidemiological Approach

Sixty-one of the 91 federally sponsored studies (67 percent) are classified as epidemiological by the Persian Gulf Veterans Coordinating Board. The remaining 30 studies are classified as basic (20 percent), applied (10 percent), and clinical (3 percent) research. Table III.4 shows that the epidemiologic emphasis is present across most major health effects and risk factors under investigation.

**Table III.4: Number of Studies by Primary Research Focus and Study Type**

Primary research focus	Research type				Total
	Applied	Basic	Clinical	Epidemiological	
Birth and reproductive effects	0	0	0	4	4
Cancer	0	0	0	1	1
Chemical weapons	1	3	0	1	5
Depleted uranium	0	2	0	0	2
Fibromyalgia	0	0	0	1	1
Gastrointestinal	0	0	0	2	2
Genitourinary	0	0	0	1	1
Immunological	0	0	0	2	2
Infectious diseases	4	3	0	1	8
Methods	1	2	1	6	10
Mortality	0	0	0	2	2
Multiple symptoms/diseases	1	0	0	18	19
Muscular	0	0	0	3	3
Multiple organophosphates (including pyridostigmine bromide)	0	6	1	2	9
Neurological/cognitive	0	0	0	3	3
Oil-well fires	2	0	0	0	2
Pulmonary	0	0	0	1	1
Stress and PTSD	0	2	1	13	16
<b>Total</b>	<b>9</b>	<b>18</b>	<b>3</b>	<b>61</b>	<b>91</b>

### Little Research on Treatment

As indicated in table III.5, federal research is currently centered on studies of the prevalence, nature, and risk factors associated with veterans' illnesses. Few studies are focusing primarily on identification and

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improvement of treatments for Gulf War veterans' illnesses. Results of our interviews with principal investigators of ongoing epidemiological projects are generally consistent with this distribution; none of the investigators we interviewed identified the primary goal of his work as developing treatment strategies.

**Table III.5: Primary Emphasis of 91 Federally Sponsored Research Projects Identified by PGVCB**

<b>Objective</b>	<b>Number</b>	<b>Percent<sup>a</sup></b>
Prevalence	26	29
Nature	17	19
Cause	18	20
Diagnosis	6	7
Treatment	3	3
Methodology	14	15
Combination	7	8

<sup>a</sup>The individual percentages do not add to 100 due to rounding.

Source: GAO analysis of information provided by PGVCB.

Descriptive studies are useful for providing information about an illness. But the principal value of doing descriptive studies is to aid in generating hypotheses that, through careful analytical studies, can lead to isolating the nature of the illness and developing treatments. Because so little was initially known about Gulf War veterans' health, there was a need for descriptive studies. Most of the epidemiological studies thus far have focused on descriptive studies of prevalence. With the exception of the studies that explore the hypothesis that combat stress explains a portion of Gulf War veterans' symptoms, research has, by and large, been stuck at the beginning of the study cycle presented in appendix I, perhaps partly as a result of a failure to identify hypotheses for further testing, the absence of exposure data, and a failure to identify one or more case definitions.

If research on treatments must follow the descriptions of illnesses and causes provided through epidemiological research, then improved treatments for the illnesses afflicting Gulf War veterans might never be found. In 1994, Congress directed DOD and VA to research treatments for ailing Gulf War veterans. Our report shows that such research has largely not taken place, even though more focused research can be done without having first answered general descriptive questions.



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## Formidable Methodological Problems

Our review indicated that most of the ongoing epidemiological studies focusing on the prevalence or causes of Gulf War-related illnesses have been hampered by data problems and methodological limitations and consequently may not be able to provide conclusive answers in response to their stated objectives, particularly in identifying risk factors or potential causes.

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## Problems With Prevalence Studies

All but one of the research objectives identified by PGVCB (as noted earlier in table III.1) concern establishing the prevalence of symptoms, exposures, morbidity, or mortality. In fact, the PGVCB research plan states that “the most important question about the health of Persian Gulf veterans is: Are Persian Gulf veterans experiencing a greater prevalence of symptoms and illnesses in comparison with an appropriate control population?” The research plan suggests that the direction of additional exploration is contingent on the answer to this question (for example, greater priority will be given to investigating excess health outcomes).

It should be noted that Gulf War veterans, even in theater, may have experienced broadly different sets of circumstances and exposures. For example, according to press reports, none of the French troops have complained of similar illnesses. Some notable differences were that French forces were not in the same places as the other allied forces; the French camps were not sprayed with insecticides; and the French did not vaccinate against anthrax, take preventive measures against botulinum toxin, or administer pyridostigmine bromide. None of the federally funded studies used French troops as a comparison group. In contrast, most of the ongoing studies designed to assess the prevalence of various conditions of Gulf War veterans and others were making broad comparisons between deployed and nondeployed veterans, rather than specific types and levels of exposures. For example, our interviews found that 12 of 13 ongoing cohort studies had defined the exposed cohort with reference to nothing more than deployment status. That is, in almost all cases, the exposure of interest was defined simply as “Gulf War service,” and the prevalence of symptoms or illnesses among Gulf War veterans is being compared to the prevalence of symptoms or illnesses among troops who were not deployed to the Gulf.

Such comparisons may have value for providing basic assurances to veterans regarding widespread and severe health consequences of Gulf War service. However, many service-connected illnesses could be obscured by broad comparisons of deployed and nondeployed veterans

without regard to their specific exposure histories. At the same time, illnesses that were not actually service connected could appear to be linked to deployment status due to preexisting group differences. For example, some troops were not deployed for health reasons, potentially biasing the comparison group in the direction of greater illness. Also, due to the failure to compare the prewar health of the groups, the absence of differences is no assurance that one of the groups has not experienced a significantly steeper decline in health.

Some investigators have attempted to address some of the problems of systematic differences between deployed and nondeployed veterans by comparing Gulf War veterans to servicemembers who were deployed to locations other than the Gulf. To the extent that such group differences are measured, they can also be statistically controlled. While these are potentially promising solutions, such comparisons must still be carefully evaluated in the absence of evidence of prior similarity between the groups and greater specificity regarding exposure.

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### Problems With Studies of Risk Factors or Causes of Illness

As we noted earlier, to ascertain the causes of illnesses, it is imperative that investigators have valid and reliable methods to collect information on exposures as well as their effects. The need for accurate, dose-specific information is particularly critical for low-level or intermittent exposure(s) to drugs, chemicals, or biological agents. In addition, the investigators must specify diagnostic criteria to (1) reliably determine who has the disease or condition being studied and who does not and (2) select appropriate controls (people who do not have the disease or condition). To the extent that individuals are misclassified regarding disease or exposure, conclusions would be misleading and relationships would be obscured.

### Measurement of Exposure Is Problematic

The research program to answer basic questions about the illnesses that afflict Gulf War veterans has at least three major problems in linking exposures to observed illness or symptoms. First, it is extremely difficult to gather information about the unplanned exposures (for example, oil-fire smoke and insects) that may have occurred in the Gulf, and DOD has acknowledged that records of planned or intentional exposures (for example, the use of vaccines and pyridostigmine bromide to protect against chemical/biological warfare agents) were inadequate. Second, the veterans were typically exposed to a wide array of agents with commonly accepted health effects, making it difficult to isolate and characterize the effects of individual factors or study their combined effects. Third, the

passage of time following these exposures has made it increasingly difficult to have confidence in any information gathered through retrospective questioning of veterans.<sup>37</sup>

In part, the latter difficulty was created by the delayed release of information about detection of chemical warfare agents during the war as well as the delayed collection of exposure data. Five years passed before it was acknowledged that American soldiers may have been exposed to chemical warfare agents shortly after the war ended in 1991 (at the Khamisiyah site). Moreover, although chemical detections by Czech forces have been deemed “credible” by the Central Intelligence Agency (CIA), the source of these detections remains unknown. In the face of denials by DOD officials, a few researchers told us that they had considered it pointless to pursue hypotheses that the symptoms may have been associated with exposure to chemical weapons.

When we asked investigators responsible for ongoing federally funded epidemiological projects about how they were collecting data on the various factors to which Gulf War veterans may have been exposed, we found that most projects had no means other than self-reports for measuring most of the factors to which troops may have been exposed. (See table III.6.) This reliance on self-reports was present even for exposures such as vaccines for which records might have existed.

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<sup>37</sup>Large numbers of veterans questioned during their participation in the VA's revised health registry examination program reported they did not know whether they were exposed to certain agents. “Don't know” responses were greatest for nerve gas (64.9 percent), mustard gas (60.2 percent), depleted uranium (52.5 percent), chemical-agent resistant coating (47.8 percent), microwaves (32.8 percent), paints or solvents (24.9 percent), and pyridostigmine (21.1 percent). To the extent that a response of some kind reflects greater certainty, veterans were more confident in their reports regarding smoke from tent heaters, passive smoking, diesel or other petrochemical fumes, skin exposure to fuel, pesticides in cream or spray form, and burning trash or feces, each of which resulted in fewer than 11 percent of respondents reporting “don't know.” However, the provision of a response does not necessarily connote that the reports are accurate.

**Appendix III  
Federal Strategy to Research Gulf War  
Illnesses Lacks a Coherent Approach**

**Table III.6: Ongoing Epidemiological Studies Using Measures Other Than Self-Reports to Assess Key Exposures**

Exposure	Is the study collecting data on this exposure? <sup>a</sup>			Is the exposure measured through any means other than self-report? <sup>b</sup>		
	Yes	No	No response	Yes	No	No response
CARC	10	10	2	1	7	2
Biological warfare agents	10	9	3	4	3	3
Depleted uranium	14	6	2	2	8	4
DEET	11	7	4	1	7	3
Permethrin	11	7	4	1	7	3
Other pesticides or repellents	12	5	5	1	8	3
Pyridostigmine bromide	15	5	2	0	11	4
Vaccines	13	5	4	6	4	3
Petroleum products	14	5	3	4	7	3
Oil-fire smoke	16	5	1	3	11	2
war stressors	15	5	2	1	10	4
Infectious diseases	11	7	4	6	5	0
Chemical warfare agents	15	4	3	5	5	5

Note: The survey incorporated responses from 31 of the 43 studies identified as ongoing epidemiological studies by PGVCB in its November 1996 plan. Of these, 22 indicated they were collecting exposure information.

<sup>a</sup>Among the 22 collecting any exposure data.

<sup>b</sup>Among those collecting data on the exposure named in the first column.

Source: GAO's survey of investigators charged with ongoing epidemiological studies.

There are three problems associated with reliance on self-reports for exposure assessments. First, recalled information may be inaccurate after such a long time period; that is, some veterans may not remember that they were exposed to particular factors, while others may not have been exposed but nonetheless inaccurately report that they were. Second, recollections also may be biased if, for example, veterans who became sick following the war recall their exposures earlier, more often, or differently than veterans who did not become sick. Third, there is often no straightforward way to test the validity of self-reported exposure information, making it impossible to separate biased recollections from actual differences in exposure frequency.

Case Definition Is Complicated  
by Presence of Nonspecific  
Symptoms

Some investigators are also relying on a model developed by the U. S. Army Environmental Hygiene Agency for assessing exposures to components of oil-fire smoke through the combination of unit location data and information from models of the distribution of oil-fire smoke. However, this method requires the use of unit location as a proxy for exposure, and the validity of this approach is unknown. As PAC noted, DOD's Persian Gulf Registry of Unit Locations "lacks the precision and detail necessary to be an effective tool for the investigation of exposure incidents." (See PAC's Final Report (Washington, D.C.: GPO), p. 35.)

Another major hurdle to the development of a successful research agenda has been the difficulty in classifying symptoms into one or more distinct illnesses. Some veterans complain of gastrointestinal pain, others report musculoskeletal pain or weakness, and still others report emotional or neurological symptoms. As explained previously, a specific case definition is essential to conducting certain types of epidemiological studies.

Although some data on symptoms were collected beginning in 1992 with the initiation of the VA registry, initial efforts to collect information about symptoms and exposures from registry participants were limited and nonspecific, constraining their potential use for improving understanding of the patterns of veterans' complaints. The limitations in early registry data are unfortunate insofar as detailed information about symptoms and exposures might have yielded earlier, more reliable analyses of the nature and causes of veterans' complaints that could have also assisted in arriving at working case definition(s). Furthermore, clinical effects of a transitory nature that may have been manifested soon after the war would have been missed due to delays in setting up and developing studies and registries.

We also found that both the federally supported projects and the federal registry programs have generally failed to study the conjunction of multiple symptoms in individual veterans. Articles and briefing documents that we have obtained report findings that address the incidence of single symptoms and diagnoses. There are two exceptions. First, the Center for Disease Control (CDC) and Prevention developed an operational case definition, which is quite similar to the case definition of chronic fatigue syndrome. Obviously, this definition cannot be generalized beyond the population from which it was derived. Second, the studies conducted by Haley et al. also focused on identifying symptom clusters.

For those ongoing epidemiological projects that are built on case-control designs, we inquired about how a case was defined. The specificity of this

definition is important because a vague case definition can lead to considering multiple kinds of illness together. When this is done, it is not surprising to find no commonality of experience among the cases. Moreover, the use of specific case definition is particularly critical to achieving meaningful results within this type of research design. However, in the ongoing studies we surveyed, case definition was quite broad, even among studies that depended upon case-control research designs. For example, among 13 case-control or nested case-control studies, case definitions included such broad descriptors as registry participants, Gulf War veterans who are symptomatic without diagnosable illness, and veterans with complaints of chronic fatigue and muscle weakness.

#### Sample Size

Most investigators we interviewed in our survey took steps to estimate the size of sample they would require to have a reasonable expectation of detecting differences between deployed and nondeployed veterans or exposures to hazardous substances. However, many variables are involved in such calculations, for example, the size of the investigated exposure's expected impact on health (consistent lethal effects can be detected in a smaller sample than more subtle problems) and the prevalence of exposure, some of which were unknown at the time the studies were planned. Thus, they had to be estimated within somewhat broad parameters. Although steps were clearly taken to plan for an adequate sample size, some investigators reported difficulty in locating subjects due to factors beyond their control, such as the rate of referrals from VA examination centers or the rate of identification of subjects that fit highly specific case definitions. Moreover, other studies, such as those on specific birth defects, require extremely large samples. An investigator on a principal study of birth defects indicated that the number of births to Gulf War veterans and problems with data collection would mean that data would not be sufficient to draw conclusions about a particular defect (Goldenhaar syndrome) for 6 years or more.

# Support for Key Official Conclusions Is Weak or Subject to Different Interpretations

A key measure of the effectiveness of a research program is the extent to which it has yielded verifiable conclusions regarding the subject of study. We previously reviewed findings contained in the November 1996 revision of *A Working Plan for Research on Persian Gulf Veterans' Illnesses* and concluded that PGVCB had formed few strong conclusions based on the research that it had sponsored and coordinated. To gauge the extent of knowledge about Gulf War illnesses, we also reviewed other recent documents and spoke to VA and DOD officials to determine what would represent the best statement of conclusions. This review indicated that the most extensive and detailed review of the evidence about Gulf War illnesses was done by the Presidential Advisory Committee on Gulf War Veterans' Illnesses. The 12-member Committee held 18 public meetings between August 1995 and November 1996 before reaching its conclusions. In its final report, PAC presents its conclusions about the likelihood that 10 commonly cited exposure agents have contributed to the explained and unexplained illnesses being suffered by Gulf War veterans. (See table IV.1.) The PAC report was reviewed by DOD, which endorsed many of the findings.<sup>38</sup>

**Table IV.1: PAC Conclusions on Health Effects of Different Individual Exposure Agents**

Exposure agent	PAC's conclusion	Reasons	Our assessment
Biological warfare agents	"It is unlikely the health effects reported today by Gulf War veterans are the result of exposures to biological warfare agents"	"There were no verified detections of anthrax or botulinum toxin during the war. Second, stateside examination of soil samples and enzyme assays did not reveal the presence of BW agents."	We have noted the limitations of the U.S. detection capability for biological warfare agents. We agree with PAC that the effects of at least one of the agents that Iraq weaponized might not be observed for many years.

(continued)

<sup>38</sup>In endorsing PAC's conclusion that it is "unlikely" that the symptoms and diseases are due to exposure to agents during the Gulf War, DOD also noted that "there may still be small groups of Gulf War veterans that may have illnesses related to exposures during the Gulf War [and that DOD] will continue...our clinical investigation and research efforts." According to PAC, VA, HHS, veterans' service organizations, and individual veterans and veterans' advocates also reviewed its report. However, PAC did not provide information on the extent to which these reviewers agreed with its findings, or whether it incorporated their comments in its reports.

**Appendix IV  
Support for Key Official Conclusions Is  
Weak or Subject to Different Interpretations**

<b>Exposure agent</b>	<b>PAC's conclusion</b>	<b>Reasons</b>	<b>Our assessment</b>
Chemical warfare agents	"It is unlikely the health effects reported by Gulf War veterans today are the result of exposure to OP or mustard chemical warfare agents during the Gulf War."	"Available scientific evidence does not indicate that such long-term effects occur in humans following low-level exposures, but the amount of data from either human or animal research on low-level exposures is minimal."	We dispute this conclusion. There is evidence from various sources that chemical weapons were released at Khamisyah and elsewhere on the battlefield. Some evidence from animal and epidemiological studies documents the potential for delayed or chronic effects from such exposure. Thus, we cannot exclude the possibility that such health effects could impact exposed veterans.
Depleted uranium	"It is unlikely that health effects reported by Gulf War veterans today are the result of exposure to depleted uranium during the Gulf War."	"Toxic effects are likely to be similar to the kidney toxicity observed from inhaled or ingested uranium. To date, VA has reported no kidney toxicity among soldiers wounded by DU fragments in friendly fire episodes."	We have no comment on this issue. <sup>a</sup>
Infectious diseases	"It is unlikely that infectious diseases endemic to the Gulf region are responsible for long term health effects in Gulf War veterans, except in a small, known number of individuals."	"While viscerotropic leishmaniasis can be difficult to confirm, it is not considered to be a cause of widespread illness in Gulf War veterans. All veterans diagnosed with viscerotropic leishmaniasis, except one, have experienced the signs characteristic of the disease. From August 1990 through July 1991, the U.S. Army deployed approximately 347,000 individuals to the Gulf region. Based on information from U.S. Army field hospitals, the only infectious diseases that caused 30 or more each of approximately 14,000 admissions were pneumonia, intestinal infections, inflammation of the testes and/or epididymus, chicken pox, and kidney infections."	Owing to the invasive character of current screening tests for viscerotropic leishmaniasis it has been impossible to test broadly for infection. Although some sources have suggested that the rate of leishmania infection may be as high as 5% of certain groups deployed to the Persian Gulf, there is currently no means of screening for asymptomatic infections which can re-emerge during immune system failure. The Center for Disease Control and Prevention has found evidence of previous Q fever and sandfly fever infection in a subsample of Gulf War veterans, which would indicate exposure to the sandfly that carries leishmania.
Oil-well fire smoke	"It is unlikely exposure to oil-well fire smoke is responsible for symptoms reported today by Gulf War veterans."	"Toxic gases that can be found in oil-well fire smoke-such as hydrogen sulfide and sulfur dioxide-can cause eye and nose irritation, decreased pulmonary function, and increased airway reactivity. These toxic gases were not detected at high levels during the fires."	We have no comment on this issue. <sup>a</sup>

(continued)



**Appendix IV  
Support for Key Official Conclusions Is  
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<b>Exposure agent</b>	<b>PAC's conclusion</b>	<b>Reasons</b>	<b>Our assessment</b>
Pesticides	"It is unlikely that health effects and symptoms reported today by Gulf War veterans are the result of exposure to pesticides during the Gulf War"	"According to DOD, after-action reports from in-theater medical personnel did not reveal any U.S. troops reporting symptoms that would indicate pesticide poisoning. Evidence from studies of humans poisoned by organophosphate pesticides suggests that low-level exposures that do not cause signs and symptoms of immediate and severe poisoning will not result in long-term health effects."	Our review of the literature identified evidence that exposure to organophosphate agents can induce delayed neuropathy without causing immediate symptoms. Moreover, it has been suggested that treatment with pyridostigmine bromide following exposure to organophosphates (either OP pesticides or chemical weapons) may actually enhance the potential for delayed effects.
Petroleum products	"It is unlikely that health effects reported today by Gulf War veterans are due to exposure to petroleum products during the war."		We have no comment on this issue. <sup>a</sup>
Psychological and physiological stress	"Stress is likely to be an important contributing factor to the broad range of illnesses currently being reported by Gulf War veterans." "The entire federal research portfolio should place greater emphasis on basic and applied research on the physiologic effects of stress and stress-related disorders."	"Animal studies demonstrate that stress can have measurable effects on the brain, immune system, cardiovascular system, and various hormonal responses. Although the human body can adapt to normal stresses, if the stress lasts longer it can be expressed in a variety of physical illness symptoms. Some researchers suspect that the inadequate production of stress hormones and stress response occurs in some (not all) humans with chronic fatigue syndrome and post-traumatic stress disorder. Based on this understanding and supported by decades of clinical observations, physicians recognize that many physical, as well as psychological, diagnoses are the consequences of stress."	Although the evidence that we reviewed indicates that stress can have an important role in symptoms of many physical illnesses, when stress is present in a patient with untreated and undiagnosed diffuse physical symptoms, care must be taken to determine whether the stress is the cause or the effect of the physical symptoms. We found weak support for the conclusion that stress is an important contributing factor in the broad range of illnesses being reported by Gulf War veterans; most of the evidence cited by PAC addressed the effects of stress solely on PTSD.

(continued)

**Appendix IV  
Support for Key Official Conclusions Is  
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<b>Exposure agent</b>	<b>PAC's conclusion</b>	<b>Reasons</b>	<b>Our assessment</b>
Pyridostigmine bromide	"It is unlikely that health effects reported today by Gulf War veterans are the result of exposure simply to PB (emphasis added). Ongoing federally funded studies should help the scientific community draw conclusions about the synergistic effects of PB and other risk factors."	PB is used in much higher doses in patients with myasthenia gravis than was administered to military personnel.	Experiments in animal models (including one study sponsored by DOD) show that PB has toxic effects in combination with other elements, such as DEET and permethrin, in the Gulf War environment. This may be particularly true for animals with a genetic predisposition. Cases of such delayed neurotoxic effects in humans exposed to PB and DEET have been epidemiologically inferred and reproduced in hens. We note that PB was intended for use only when other agents were believed to be present or imminent. PB remains classified as an investigational new drug for the purposes for which it was used in the Gulf War.
Vaccines	"It is unlikely that health effects reported by Gulf War veterans today are the result of exposures to the BT or anthrax vaccines, used alone or in combination."	"The human immune system has evolved the capability to deal with thousands of foreign substances, to sort them out, and to regulate immune response. Humans live among a vast population of hostile microorganisms, and vaccinations—even multiple, contemporaneous vaccinations—are a small part of total immune stimulation. Individual vaccines can cause adverse effects, but several studies of the effects of giving multiple vaccinations at one time have found no adverse effects associated with the practice."	DOD has not adequately monitored the effects of receiving multiple vaccines.

<sup>a</sup>This does not mean that we believe that it is not a risk factor.

## Extent of Posttraumatic Stress Disorder May Be Overestimated

PGVCB has stated that "some symptoms may be related to PTSD. Published findings suggest an increased prevalence of PTSD and other psychiatric diagnoses, such as depression in some Persian Gulf veterans....stressors during the Persian Gulf conflict were sufficient to cause significant psychiatric morbidity."<sup>39</sup> In testimony before the House Appropriation Committee, the Assistant Secretary of Defense for Health Affairs has stated that

<sup>39</sup>PGVCB, *A Working Plan for Research on Persian Gulf Veterans' Illnesses* (Nov. 1996), p. 36.

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**Appendix IV**  
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“one of the most striking findings of our clinical work has been the recognition of psychological conditions and stress-related symptoms as a major diagnostic category among veterans cared for in our facilities. Our clinicians have been impressed that stress experienced during the Gulf War and in its aftermath appears to be a major contributing factor in the development of psychological conditions as well as the manifestation of symptoms associated with non-psychological conditions.”

Similarly, PAC has stated that “epidemiological studies to assess the effects of stress invariably have found higher rates of PTSD in Gulf War veterans than among individuals in nondeployed units or in the general U.S. population of the same age.”<sup>40</sup> However, the studies to which PAC refers have not excluded other conditions that produce symptoms similar to PTSD and can also elevate scores on key measures of PTSD. Although the reported rates of PTSD in various studies range from 4 to 32 percent, these rates were based on widely different populations, with high rates of nonparticipation, and little information on selection bias. Moreover, as with most scales and tests, a certain number of people will test positive on any given measure of PTSD even though they do not have PTSD; they may have a related disorder or no disorder at all. Based on the large numbers of individuals to whom these scales were administered, such false positives may be a significant portion of all those who obtained scores indicative of PTSD. In a CDC-sponsored study of Iowa veterans that achieved a 76-percent response rate and used a relatively inclusive criterion for identification of presumptive PTSD, observed rates were quite low, although they were higher among Gulf-deployed than nondeployed veterans.<sup>41</sup>

Only 15 percent of the diagnoses categorized as psychological (according to the International Classification of Diseases-9th Revision (ICD-9)) among CCEP registrants are clear cases of PTSD. Owing to the breadth and heterogeneity of ICD-9 categories used to report CCEP data, high percentages of primary or secondary “psychological conditions” are reported, but the most frequently diagnosed “psychological condition” was tension headache. Investigators from the Department of Military Psychiatry at WRAMC reported, “The major conclusion concerning physical health of these veterans is that for those who deployed to the Gulf War and currently report physical symptoms, neither stress nor exposure to combat

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<sup>40</sup>PAC, *Final Report* (Dec. 1996), p. 79.

<sup>41</sup>Iowa Persian Gulf Study Group, “Self-reported Illness and Health Status Among Gulf War Veterans: A Population Based Study,” *Journal of the American Medical Association*, vol. 227 (1997), pp. 238-245.

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or its aftermath bear much relationship to their distress; only the fact of deployment differentiates them from their less-burdened counterparts.”<sup>42</sup>

Alternative causes for stress-related symptoms may not have been fully explored. For example, just following the war, experts from Walter Reed Army Institute of Research (WRAIR) and WRAMC noted,

“Sandfly fever (phlebotomus fever)....has caused substantial epidemics in foreign military forces in the Middle East. It is an acute, self-limited viral disease with a course of two to five days and an incubation period of less than one week, whose acute manifestations will be unlikely in those who have returned from the region. Convalescence, however, is frequently complicated by depression, fatigue, and weakness that can last months. The evaluation of a chronic fatigue or post-traumatic stress-like syndrome in those who have returned from the Persian Gulf should therefore include serologic testing to rule out an earlier sandfly fever virus infection.”<sup>43</sup>

Such serologic testing is available only from CDC, in Fort Collins, Colorado, and from U. S. Army Medical Research Institute of Infectious Disease (USAMRIID) in Fort Detrick, Maryland. Thus, it is unlikely that testing has been broadly done to assess veterans’ fatigue symptoms. However, a CDC analysis of blood taken from 158 volunteer Pennsylvania Air National Guardsmen found that 5.7 percent showed evidence of previous sandfly fever infection. For various reasons, including false positives and the absence of preexposure blood samples for comparison, such evidence can be difficult to interpret but suggests the importance of reviewing alternative explanations for diagnoses of PTSD and chronic fatigue syndrome.

Although widely cited work has argued that ill-defined syndromes have been observed following many previous military conflicts, it is difficult to compare current and historical findings due to differences in the diagnostic capabilities previously available.<sup>44</sup> It is highly likely that these historical groups contained a mix of ailments that would now be differently diagnosed. Moreover, even if these postwar syndromes contained overlapping symptoms, it is not a foregone conclusion that commonalities reflect the common experience of stress.

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<sup>42</sup>R. H. Stretch et al., “Physical Health Symptomatology of Gulf War-era Service Personnel From the States of Pennsylvania and Hawaii”, *Military Medicine*, vol. 160 (1995), pp. 131-136.

<sup>43</sup>R. A. Gasser et al., “The Threat of Infectious Disease in Americans Returning From Operation Desert Storm,” *The New England Journal of Medicine*, vol. 324 (1991), p. 862.

<sup>44</sup>K. C. Hyams et al., “War Syndromes and Their Evaluation: From the U.S. Civil War to the Persian Gulf War,” *Annals of Internal Medicine*, vol. 125 (1996), pp. 398-405.

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## Extent of Asymptomatic Leishmania Infection Is Unknown

PGVCB concluded that "the likelihood of *Leishmania tropica* as an important risk factor for widely reported illness has diminished."<sup>45</sup> While this is the case for observed symptomatic infection with the parasite, the prevalence of asymptomatic infection is unknown, and such infection may reemerge in cases in which the patient's immune system becomes deficient.

Leishmaniasis is an infectious disease caused by a microscopic parasite that invades certain types of white blood cells. While leishmaniasis occurs in Southwest Asia and certain other parts of the world, it is very rarely seen in the United States. The disease is transmitted by sandflies, and a number of different leishmania species are known to infect humans. Personal protective methods are relatively less effective against sandflies than against mosquitoes. Sandfly populations were monitored during the Gulf War and were found to be high from August to November 1990 and again from April to June 1991.

Forms of disease that involve low levels of parasite infection can be particularly difficult to diagnose using currently available methods. According to briefings we received by experts at WRAIR, accurate diagnosis of leishmaniasis is important because effective treatment involves the use of potentially toxic drugs currently being investigated as new drugs and not yet approved by the Food and Drug Administration. They noted that such diagnosis is problematic because

- most clinicians would fail to recognize classic forms of leishmaniasis, much less atypical clinical presentations;
- accurate laboratory diagnosis of suspected cases (detection of parasites in biopsy or culture) is not available to most physicians; and
- blood tests can provide supportive evidence of infection but cannot be used alone to establish a diagnosis of leishmaniasis.

While blood testing for leishmania infection is problematic, it is the only means currently available of assessing the potential prevalence of such infection. In testing blood collected since the war from 158 Air National Guardsmen, CDC researchers reported positive results for exposure to

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<sup>45</sup>PGVCB, *A Working Plan for Research on Persian Gulf Veterans' Illnesses* (Nov. 1996), p. 20.

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**Appendix IV**  
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leishmania donovani in 4.9 percent and leishmania tropica in 4.3 percent.<sup>46</sup> Most of these individuals were also among the 5.7 percent showing evidence of exposure to the sandfly vector that carries leishmania through positive results on a well-characterized test for sandfly fever. However, the CDC sample was composed of Air National Guardsmen who volunteered for a particular study and were deployed from the same area, so the tests do not represent estimates of the prevalence of the infection for Gulf War veterans at large. The study also found no clear association between results for leishmania infection and the presence of a set of symptoms characteristic of chronic fatigue syndrome.<sup>47</sup>

Although PGVCB officials told us that the symptoms typical of leishmaniasis, including enlargement of the liver, were not being observed, not all ill veterans would show such symptoms. In commenting on a report on a new form of leishmaniasis, CDC noted that five Gulf War veterans had been diagnosed with the infection, even though their symptoms were nonspecific, and none had the marked symptoms typical of visceral leishmaniasis.<sup>48</sup> Approval continues to be pursued for a skin test to assess the prevalence of asymptomatic infection.

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<sup>46</sup>In 1991, tests were run on blood samples from 119 military working dogs that had been in Saudi Arabia. Five dogs (4.2 percent) were positive for the disease. One of these dogs subsequently developed the infection, which was confirmed by autopsy. Symptomatic disease and demonstrated infection have been observed in individuals with serological titers of 1:16. While none of 50 Marines showed a result at this level before deployment, tests of 488 Desert Storm veterans conducted after the war showed 5 percent had results of 1:32 or higher. Roughly 5 percent of a sample of troops tested after the initial identification of viscerotropic leishmaniasis showed positive results using a skin test involving a slightly different parasite. However, few of those who tested positive were symptomatic, and the accuracy and appropriateness of the tests for this purpose is controversial. Finally, a Seattle organization attempting to develop a test for viscerotropic leishmaniasis has reportedly found positive responses among asymptomatic subjects. WRAIR officials view this test as a highly specific indicator of exposure to leishmania tropica, but not a specific indicator for the type of the parasite associated with viscerotropic infection.

<sup>47</sup>Based on concerns about the potential for transmission of this disease through the blood supply, blood donations were temporarily deferred for all Gulf War veterans returning from Southwest Asia since August 1, 1990. The blood donation ban was lifted on January 1, 1993. However, an accurate and noninvasive screening test for this form of leishmaniasis remains commercially unavailable. Although a study of transfused animals has demonstrated that the parasite retains its infectivity under blood bank conditions, in lifting the ban, DOD officials observed that there had been no documented case of transfusion-acquired leishmania tropica.

<sup>48</sup>"Viscerotropic Leishmaniasis in Persons Returning from Operation Desert Storm—1990-1991," *MMWR*, vol. 41, pp. 131-134. Reprinted in *Journal of American Medical Association*, vol. 267(11) (1992), pp. 1444-46.

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## Evidence of Exposure to Biological and Chemical Weapons Has Not Been Aggressively Pursued

DOD has consistently denied that Gulf War veterans were intentionally or unintentionally exposed to biological warfare agents, and prior to June 1996, it denied any exposure to chemical warfare agents. If servicemembers were exposed, exposure would have occurred in one of three ways: (1) through intentional Iraqi use of chemical or biological warfare agents, (2) through theaterwide contamination resulting from air war bombings of Iraq, or (3) through site-specific events.

As has been pointed out by the Presidential Advisory Committee, the United States currently has no system that can detect and identify biological warfare agent aerosols rapidly enough to enable troops to take protective measures. Regarding chemical warfare agents, while the United States has a detector/alarm system, according to DOD, it is not as sensitive as some other systems, such as those operated by Czechoslovakian coalition partners. DOD has taken the position that chemical and biological agent exposures can be confirmed only through evidence of mass incidents of morbidity and mortality. Since there were no such instances, DOD asserted that Gulf War veterans were not exposed.

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## Biological Warfare Agents

According to the CIA, the Presidential Advisory Committee, and others, the Iraqis had weaponized several biological agents at the time of the Gulf War, including *Bacillus anthracis*, *Clostridium botulinum*, and aflatoxin.<sup>49</sup> Apart from aflatoxin (a potent liver carcinogen), these agents are known to have immediate and life-threatening toxic effects. Although the United States took steps to vaccinate troops against anthrax and botulism, according to PAC, "after the war, new data revealed that Iraq had also weaponized aflatoxin." This agent's effects may not be observed until decades after low-level exposure via ingestion, and the effects of aerosolized aflatoxin are poorly understood. PAC notes that any effects (notably liver cancer) from exposure to aflatoxin would not be expected until several years passed. PAC also recommended that DOD and VA monitor the Gulf War veteran population.

PAC reviewed U.S. Army hospital admission records and identified only one admission for anthrax (a disease indigenous to the Gulf region) and none for botulism. In addition, although Navy and Army researchers tested over 800 pairs of prewar and postwar blood samples from Navy Seabees for antibody to anthrax, they found no evidence of acute infections. While many blood samples showed evidence of vaccine-induced immunity, only

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<sup>49</sup>J. D. Walker, "Biological Weapons: Attempts to Verify" In Ranger, R. (Ed.) (1996). *The Devil's Brews I: Chemical and Biological Weapons and Their Delivery Systems* (Lancaster, UK: The Center for Defence and International Security Studies), pp. 36-8.

one showed evidence of exposure to the wild antigen or similar bacteria. PAC reported that other evidence it examined also failed to support the notion that biological weapons were used.

The PAC report documents that Iraq had weaponized aflatoxin. In our discussions with agency officials, the potential use of aflatoxin was dismissed because it would not immediately incapacitate coalition forces and would therefore have no strategic value. Prior to the war, the United States told Iraq that any use of biological or chemical weapons on coalition forces would have devastating consequences for Iraq. The United States did not deploy a real-time detection system for biological weapons.<sup>50</sup> Therefore, one cannot be certain that such weapons were not used, particularly since the United Nations Special Commission on Iraq (UNSCOM) has not been able to confirm Iraq's self-declared destruction of these weapons.<sup>51</sup>

Similarly, a USAMRIID official indicated that tests were not available to detect low-dose (i.e., asymptomatic) exposures to various biological agents that the Iraqis had weaponized. While biomarkers may be available for exposure to some of these agents, interpreting the results of such testing in the absence of symptoms is complex, and little such testing appears to have been done.

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## Chemical Warfare Agents

As with exposures to biological weapons, there were no massive incidents of mortality or morbidity observed in theater that were consistent with known acute effects of exposure to chemical warfare agents. The U.S. Army officer responsible for medical surveillance of chemical/biological warfare agents during the war has testified to the PAC that only one accidental casualty was treated. However, it is important to note that detections of the nerve agent sarin occurred on January 19, 1991, and of mustard gas on January 24, 1991, by coalition partners from Czechoslovakia in areas near Hafir al Batin. DOD has verified the reliability

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<sup>50</sup>The Army fielded the interim Biological Integrated Detection System (BIDS) in September 1996. A total of 38 systems have been produced, with a total of 35 located collectively with the 310th Army Reserve Chemical Company (Biological Detection) and the 20th BIDS Detachment (Active Army), at Ft. McClellan, AL. The current BIDS can detect and identify up to four biological agents at a time in 45 minutes. Future improvements are expected to enable BIDS to detect and identify more agents in less time. (Sources: Chemical and Biological Defense: Emphasis Remains Insufficient to Resolve Continuing Problems (GAO/NSIAD-96-103, Mar. 29, 1996), p.6; Chemical and Biological Defense: Protection of Critical Overseas Ports and Airfields Remains Largely Unaddressed (GAO/NSIAD-97-9, June 13, 1997), pp. 20-21.

<sup>51</sup>See Chemical and Biological Defense: Emphasis Remains Insufficient to Resolve Continuing Problems (GAO/NSIAD-96-103, Mar. 29, 1996).



of the Czech equipment but has never identified the source of these detections, although both DOD and CIA have deemed the detections credible. One cannot rule out the possibility that these detections were the result of fallout from coalition bombings.

During late January and February 1991, DOD records indicate that coalition forces successfully conducted a series of aerial bombings on suspect nuclear, biological, and chemical weapons storage and production sites. UNSCOM has not inspected all suspect and targeted sites. As a result, the magnitude of exposures to chemical warfare agents has not been fully resolved.

With regard to site-specific exposures identified at Khamisiyah, uncertainties surround the extent of potential exposure. A contractor for CIA had attempted to model the dispersion of chemical warfare agents. But the uncertainties were too great to complete the model. These uncertainties stem from (1) the lack of pertinent meteorological data; (2) gross uncertainties about the amount of chemical warfare material present at the time of demolition; and (3) the behavior of the material on demolition (e.g., vaporization or evaporation) in an open pit.

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## Impact of DOD Denials on Federal Research

The 1995 PGVCB research plan noted that investigations of chemical weapons effects were not done because there was no evidence of exposure.<sup>52</sup> Noting that there had been no mass casualties to indicate chemical weapons exposure, DOD failed to fund research on the possible long-term health consequences of low-level exposure to chemical warfare agents. In fact, a few researchers told us that, as a result of DOD's strong position, they believed it would be fruitless to request funding for such research. PGVCB reversed its position in its 1996 plan, following the revelations regarding Khamisiyah. A broad agency announcement seeking research on this issue was subsequently issued and some work has been commissioned. Experts in the field of toxicology told us that had such information been made available earlier, the direction and outcome of research would have been different.

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<sup>52</sup>We could not assess this statement, as relevant data were not available for us.

# Comments From the Department of Defense

Note: GAO comments supplementing those in the report text appear at the end of this appendix.



HEALTH AFFAIRS

THE ASSISTANT SECRETARY OF DEFENSE

WASHINGTON, D. C. 20301-1200

JUN 9 1997

Mr. Henry L. Hinton, Jr.  
Assistant Comptroller General  
National Security and International Affairs Division  
U.S. General Accounting Office  
Washington, DC 20548

Dear Mr. Hinton:

This is the Department of Defense (DoD) response to the General Accounting Office (GAO) draft report, "GULF WAR ILLNESS(sic): Improved Monitoring of Clinical Progress and Re-examination of Research Emphasis Needed," dated May 19, 1997 (GAO Code 713002), OSD Case 1364. The DoD only partially concurs with the draft report. While the thrust of some of the recommendations has merit, the report suggests some misunderstanding of both DoD clinical and research programs and the role these programs play in understanding Gulf War veterans' illnesses. More importantly, the recommendations do not fully take into account the complex set of health outcomes related to the Gulf War and fail to recognize the significant accomplishments of the Department as noted by the Institute of Medicine and Presidential Advisory Committee.

Preceding this GAO report, there have been several independent assessments of Gulf War veterans' illnesses and the DoD and VA research and clinical programs. The Institute of Medicine, in independent reviews, concluded that: "The DoD has made conscientious efforts to build consistency and quality assurance into this program at the many medical treatment facilities and regional medical centers across the country. This nationwide effort was implemented relatively quickly. The committee commends the DoD for its efforts to provide high-quality medical care in the Comprehensive Clinical Evaluation Program (CCEP) and the success it has achieved to date in developing the infrastructure necessary to efficiently contact, schedule, refer and track thousands of patients through the system." "...Signs and symptoms without diagnosis or apparent cause are found in every medical practice; clinical medicine is neither perfect nor all-knowing. Although physicians may fail to provide a medical reason for some of these signs and symptoms, the illnesses and related disability have to be addressed as well as possible, independent of efforts to understand causes. All of us in the health care and public health fields are committed to using the scientific study methods available to us in an attempt to understand and better explain what is presently known. Only in this way can we make progress in defining, preventing and treating disease."

Appointed by President Clinton, the Presidential Advisory Committee on Gulf War Veterans' Illnesses concluded that: "...the government is...providing appropriate medical care to Gulf War veterans and has initiated research in the areas most likely to illuminate the causes of their illnesses." "...for the most part, the government has acted in good faith to address veterans'

See comment 1.

Appendix V  
Comments From the Department of Defense

health concerns.” "...the government's current research portfolio on Gulf War veterans' illnesses is appropriately weighted toward epidemiologic studies and studies on stress-related disorders that are more likely to improve our understanding of Gulf War veterans' illnesses. For the most part, the government's prioritization process has worked."

See comment 2.

This report differs from these independently derived findings, upon which much of the DoD and VA research and clinical programs are based, without having carried out the level of careful and thoughtful assessments carried out by the Institute of Medicine Committees and the Presidential Advisory Committee.

The detailed DoD comments on the GAO recommendations are provided in the enclosure. The DoD appreciates the opportunity to comment on the GAO draft report.

  
Edward D. Martin, M.D.

Acting Assistant Secretary of Defense

Enclosure:  
As stated

Appendix V  
Comments From the Department of Defense

GAO DRAFT REPORT - DATED MAY 19, 1997  
OSD CASE 1364, GAO CODE 713002

“GULF WAR ILLNESS(sic): IMPROVED MONITORING OF CLINICAL  
PROGRESS AND RE-EXAMINATION OF RESEARCH EMPHASIS NEEDED”

DEPARTMENT OF DEFENSE COMMENTS ON  
THE GAO RECOMMENDATIONS

RECOMMENDATION 1: The GAO believes that efforts to monitor Gulf War veterans' clinical status are necessary to provide direction to the research agenda and to ensure that veterans are receiving appropriate and effective treatments. Moreover, the Institute of Medicine and at least one veterans' service organization have also highlighted the importance of monitoring the progress of Gulf War veterans. We agree with these organizations and recommend that the Secretaries of Defense and Veterans Affairs develop and implement plans to monitor the clinical progress of veterans who have participated in their postwar examination programs. (p.13 / GAO Draft Report)

DoD RESPONSE: Partially concur. The DoD established the Comprehensive Clinical Evaluation Program (CCEP) as a clinical rather than a research program to provide health care to veterans who may be experiencing health problems possibly related to their service in the Persian Gulf. The CCEP process has been reviewed by a series of nationally recognized expert panels including the Presidential Advisory Committee and groups from the Division of Health Promotion and Disease Prevention - Institute of Medicine (IOM). Each of the panels included distinguished clinicians, scientists, and scholars across multiple disciplines. The IOM committees specifically commended the DoD for “its efforts to provide high quality medical care and success in developing the infrastructure necessary to efficiently contact, schedule, refer and track thousands of patients through the system.” The IOM further concluded that there is “no clinical evidence in the CCEP for a previously unknown illness among Persian Gulf veterans.” In addition to the IOM Committees, the Final Report of the Presidential Advisory Committee on Gulf War Veterans' illnesses noted, “The committee agrees with the IOM's conclusion that the clinical evaluation programs of the DoD and VA are excellent for the diagnosis and care of Gulf War veterans' illnesses.” Therefore, the Department continues to operate the CCEP and to actively collaborate with VA to share information and to plan accordingly.

In keeping with the spirit of the GAO recommendation, in November 1996, the DoD requested a draft feasibility proposal to evaluate the current health status of CCEP participants. The proposal shall specifically address measures of health outcomes of CCEP participants. A proposal has been received and is currently being reviewed. Our goal is to find health outcome measures that can reflect current health status of Gulf War veterans compared with Gulf War era veterans and other appropriate comparison groups. Some of the outcome measures may include active duty attrition rates, hospitalizations,

Enclosure

See comment 3.

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Comments From the Department of Defense

ambulatory visits, medical and physical evaluation board rates, promotion rates, and mortality rates.

Relative to the Gulf War, significant information is known regarding the nature of veterans' illnesses. In April 1994, a non-Federal, independent panel of experts sponsored by the National Institutes of Health concluded that veterans appeared to be "experiencing no single disease or syndrome, but rather multiple illnesses with various overlapping symptoms and causes." This conclusion is consistent with the subsequent clinical experience of the DoD in providing systematic clinical examinations to veterans through the Comprehensive Clinical Evaluation Program (Mil Med 1997; 162(3):149-155). Over 90,000 Gulf War veterans, approximately 13 percent of the deployed force, have elected to participate in the medical programs conducted by the Departments of Defense and Veterans Affairs.

See comment 3.

The Department embraces the contemporary approaches to utilization management, quality management, and risk management found in civilian health care and applies these approaches to all DoD beneficiaries including Gulf War veterans. Such an approach provides a more than adequate mechanism for the oversight of care provided. Whatever uncertainties may exist about the causes of Gulf War veterans illnesses, veterans are receiving appropriate and effective treatment according to standards currently in place for all patients within the DoD medical treatment facilities. The vast majority of CCEP participants have the types of diagnoses commonly seen in military and civilian primary care settings. Indeed, as in any clinical setting, the treatment of veterans in the CCEP has been according to their clinical presentation as is typical of medical practice. Finally, the fact that CCEP participants have multiple diagnoses and may see multiple providers is consistent with the experience of other health care beneficiaries. Gulf War veterans have been treated according to the same high standards of care provided to all beneficiaries within the Military Health Services System.

Nonetheless, many conditions such as chronic fatigue syndrome or depression are chronic and do not lend themselves to time-limited resolution. Civilian as well as military patients suffering from these conditions may have symptoms that persist for years. It should be noted that the DoD provides intensive follow-up to those individuals from the CCEP who require care beyond the CCEP evaluation. Specifically, at the Walter Reed Army Medical Center's Specialized Care Program, follow-up occurs at the 3, 6, 9, and 12 month intervals upon completion of the program.

All military personnel are afforded high quality comprehensive health care and follow-up in the Military Health Services System. This system of care and follow-up ensures that quality care, based on the best available medical services, is provided. The DoD has an established policy for the consolidation and expansion of centralized databases which will assess health outcomes, health care utilization patterns, and both ambulatory visits and in-patient trends. Furthermore, DoD is constructing an automated information system to monitor any medical consequence and other health-related events within individuals before, during, and after a deployment. This system will ensure

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Comments From the Department of Defense

targeted prevention and control programs for those at greatest risk of deployment-related injuries or illnesses in future deployments.

See comment 4.

The underlying theme of the GAO Report appears to be that there is a single or a few large scale Gulf War-related illnesses for which there are specific correct treatments. That conclusion is contrary to scientific evidence to date and the conclusions of at least three independent, expert scientific panels.

RECOMMENDATION 2: The GAO recommended that the Secretary of Defense, in conjunction with the Secretary of Veterans Affairs, give greater priority to research on treatment for ill veterans and on low-level exposures to chemicals and their interactive effects and less priority to further epidemiological studies. (p. 13-14 / Draft GAO Report)

See comment 5.

DoD RESPONSE: Partially concur. This recommendation appears to be inconsistent with basic clinical and research principles. Research for effective treatment(s) or clinical trials almost always follows rather than precedes the identification of illness and epidemiological studies. Clinical and epidemiologic studies in the current research portfolio have provided and shall continue to provide appropriate information for further research that shall benefit the population in question. The Medical Follow-up Agency of the IOM said specifically on page 25 of their final report, "Even when considering the difficulties and cautions in interpreting research as described above, the committee believes that there is a sound basis for epidemiologic studies..." The GAO fails to acknowledge that research results thus far have provided accurate and conclusive results regarding causes of mortality (JAMA 1996; 275 and NEJM 1996; 335), rates and causes for hospitalizations (NEJM 1996; 335), rates and types of adverse birth outcomes (Mil Med 1996; 161 and NEJM 1997; 336), as well as many other health outcomes. Well designed clinical and epidemiologic studies that compare specific health outcomes within distinct groups of individuals with appropriate comparison or control groups are extremely important and remain a valid approach to better understanding Gulf War health issues. These studies do not lose their importance if validated exposure data are difficult to obtain. The findings from these studies can help identify areas for future research.

See comment 6.

See comment 7.

In keeping with the GAO recommendation, however, DoD and VA are committed to better understanding the possible health effects of exposure to sub-clinical levels of chemical warfare agents and other environmental hazards. As of December 1996, more than \$15 million was allocated in the area of subclinical exposures to chemical warfare nerve agents and health effects from other hazardous exposures including possible interactive effects. As with all Persian Gulf-related health research managed by DoD, scientific proposals are formally solicited by an announcement in the Commerce Business Daily. All proposals are then anonymously peer-reviewed by experienced panels of independent experts and rated for scientific merit. The Research Working Group of the Persian Gulf Veterans' Coordinating Board then selects the best proposals based on scientific merit and program relevance, ensuring a balanced research portfolio across multiple fronts. We do agree that research into environmental factors is critical. Our current research effort for 1997 includes \$10 million extramural research targeted at

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possible health effects of exposure to chemical warfare agents or other toxins, as well as combinations of inoculations and investigational new drugs. An additional \$5 million of joint DoD and VA research money is committed to study stress, somatization disorders and possible health effects of exposure to subclinical chemical warfare agents.

Throughout this report, GAO has criticized the findings and recommendations of a committee of nationally recognized experts, called together by the President of the United States, to better understand the health issues of Gulf War veterans. While it would be inappropriate for the Department to comment on the GAO findings related to the Presidential Advisory Committee, we are surprised that several key Presidential Advisory Committee findings were dismissed since this expert panel conducted an extensive, 18-month investigation that included multiple field hearings.

RECOMMENDATION 3: The GAO recommended that the Secretaries of Defense and Veterans Affairs refine the correct approaches of the clinical and research programs for diagnosis of post-traumatic stress disorder consistent with suggestions recently made by the Institute of Medicine. (p. 14 / GAO Draft Report)

DoD RESPONSE: Partially concur. Both organizations have already designed and initiated clinical and research programs to better understand Post-Traumatic Stress Disorder (PTSD), as well as other stress-related health outcomes. Multiple expert panels including the Defense Science Board, National Institutes of Health Consensus Panel, two IOM panels and the Presidential Advisory Committee have all recognized that stress is an important contributing factor to the broad range of illnesses, including PTSD, being reported by Gulf War veterans. Replicated studies have shown an association between stress and PTSD and other conditions in both clinical and population studies. Given the clinical nature of the CCEP, it is not surprising that approximately 5% of CCEP participants have a diagnosis of PTSD and that this observation is higher than that reported in population based studies. In 1997, DoD and VA will publish a solicitation and commit at least \$5 million for both basic and applied stress-related research. Furthermore, DoD and VA have nationally recognized experts at medical referral centers to assist clinicians in the diagnoses and treatments related to PTSD.

The CCEP uses state-of-the-art instruments for the diagnosis of Post-Traumatic Stress Disorder and other psychological conditions. The Clinician-Administered PTSD Scale (CAPS) is the structured interview used to assess for the presence and severity of PTSD. Empirical research has shown that the CAPS is a valid and reliable instrument for this purpose and is the instrument of choice among scientists studying individuals with PTSD. The Structured Clinical Interview derived from the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) is used extensively in psychiatric research to measure psychological conditions. It was selected for use in CCEP because it provides the most accurate, comprehensive, and reproducible diagnostic assessment for psychological conditions currently available. These measures are used for all CCEP patients warranting the phase II multispecialty assessment. Patients referred for

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See comment 8.

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**Comments From the Department of Defense**

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psychological assessment undergo similarly extensive and validated neuropsychological and psychological testing.

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OFFICE OF THE SECRETARY OF DEFENSE

1000 DEFENSE PENTAGON  
WASHINGTON, DC 20301-1000



17 JUN 1997

Mr. Henry L. Hinton, Jr.  
Assistant Comptroller General  
National Security and International Affairs Division  
U.S. General Accounting Office  
Washington, D.C. 20548

Dear Mr. Hinton:

As was discussed with your staff, we are providing additional input for GAO's report, "Gulf War Illness -- Improved Monitoring and Re-examination of Research Emphasis Needed", beyond that provided in our June 9th letter. (See attachment.) Our intention in providing this input is to assist GAO in producing a factually correct and useful report for the Congress. However, its value, especially to Gulf War veterans, is heavily dependent upon being factually correct and drawing supportable conclusions from those facts. Its added value is heavily dependent upon the extent to which it builds upon and rises above the foundation laid by many preceding efforts. As for the current draft, unfortunately, very little is new.

Virtually all of these facts and conclusions, in the draft we have for review, have been surfaced before by efforts inside and outside the government. We understand well the shortcomings of the past. We have owned up to them on many occasions. But most importantly, we have taken the lessons learned and applied them both to caring for our Gulf War veterans and protecting our troops in the future.

Over the past several years, much work has been done to ensure that we take care of our Gulf War veterans, understand Gulf War illnesses and their causes, and protect our troops during future deployments. Many parties have played a constructive role in that effort, including Departments of Defense (DoD), Veterans Affairs (VA) and Health and Human Services, the Institute of Medicine (IOM) and the Presidential Advisory Committee (PAC). While much more remains to be done, much more of this multiagency effort needs to be recognized by the GAO.

With respect to the factual basis for the GAO study and the subsequent conclusions, we want to make several points.

- Since the beginning of the VA and DoD clinical programs, we have had in place systems to ensure that quality care, using the best available medical science, is being provided to our Gulf War veterans. What we are adding, as we advised the PAC some time ago, is a strategy to look at a sample of our patients and their progress over time.
- Both epidemiological studies and studies on potential causes need to be pursued aggressively. The GAO study mistakenly assumes that the difficulty in carrying out Gulf War epidemiological studies reduces their importance and continuing contribution.

FEDERAL RECYCLING PROGRAM



PRINTED ON RECYCLED PAPER

Appendix V  
Comments From the Department of Defense

- Working through the Persian Gulf Veterans Coordinating Board, the three Departments have had a coherent research plan, reviewed positively by the PAC and IOM and shared with the Congress, for quite some time. The GAO study fails to recognize that fact.
- In GAO's criticisms of "government conclusions", GAO discounts the considerable work done by the PAC and by the three Departments and overstates the extent to which the government has arrived at "conclusions." As we have stated on many occasions, our work on determining the causes of Gulf War veterans illnesses continues.

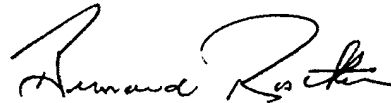
Even in the title of the report, there is no recognition of progress or commitments already made.

Again, focusing on the past and failing to acknowledge the enormous progress made does not serve well either the Congress or Gulf War veterans. We hope you will make the changes necessary for a report that is to serve well the Congress and our Gulf War veterans and their families.

Sincerely,



Edward D. Martin, M.D.  
Acting Assistant Secretary of Defense  
(Health Affairs)



Bernard D. Rostker, Ph.D.  
Special Assistant for Gulf War Illnesses

Enclosure  
As Stated

The following is GAO's response to the Department of Defense's (DOD) comments, dated June 9, 1997.

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## GAO Comments

1. DOD offers selected excerpts from reports of the Institute of Medicine (IOM) and the Presidential Advisory Committee (PAC) that leave the impression the reports were uncritical of its actions, but this was not the case. These reports point out multiple problems and contain numerous recommendations for improvement.
2. The national defense authorization act for fiscal year 1997 requested that we conduct an independent and objective review of federal clinical care and medical research efforts into Gulf War illnesses. That directive included gathering and analyzing information and coming to our own conclusions on the matters under review. Our information sources included previous reports, such as those by the IOM Committee to Review the Health Consequences of Service During the Persian Gulf War and the Presidential Advisory Committee on Gulf War Veterans' Illnesses. However, the conclusions presented in our report are ours, and not those of other bodies. DOD's assertion that our assessment was somehow less careful or thoughtful than those provided by the PAC and IOM is groundless.
3. DOD's comments do not address our specific finding that it has no information on whether Gulf War veterans are any better or worse today than when they were initially diagnosed. DOD suggests that its current approach provides adequate oversight for Gulf War veterans' care but then indicates that it is reviewing a draft proposal on health outcome measures. We found that DOD relies on quality assurance mechanisms that do not ensure a given level of effectiveness for the care provided. Given the fact that DOD has no way to track changes in veterans' health status, we continue to believe that DOD and VA should develop and implement plans to monitor the clinical progress of veterans.
4. DOD incorrectly infers that we have taken the position that a single illness or a few illnesses with specific correct treatments account for veterans' complaints. We repeatedly stated in our draft report that veterans are experiencing a wide array of symptoms and disabling conditions.
5. DOD's conclusion that research on treatments should await the results of epidemiological studies belies the fact that several illnesses suffered by these veterans have already been identified but that imperfect treatment

exists for these illnesses. Additionally, DOD and VA were directed to conduct research on treatments for ailing Gulf War veterans in the national defense authorization act for fiscal year 1995. Our report does not recommend that any ongoing research be discontinued; rather, it points out that as a result of the misplaced focus and formidable methodological problems, much of the ongoing epidemiological research will not be able to provide precise, accurate, and conclusive answers regarding the potential causes of the Gulf War veterans' illnesses. Moreover, given that the majority of federal research already covers epidemiological issues, we recommend that DOD give greater priority to research on treatment for ill veterans and on low-level exposures to chemicals and their interactive effects and less priority to further epidemiological studies.

6. IOM also commented that any additional nationwide epidemiologic studies of Gulf War veterans are likely to be of limited scientific value at this time. At this stage, greater emphasis is warranted on studies that explore plausible disease hypotheses rather than large-scale population-based studies of prevalence. While the large-scale federal studies cited by DOD have yielded descriptive information on the health profile of Gulf War veterans, they have shed less light on why Gulf War veterans report more health complaints than nondeployed veterans.

7. Regarding research on low-level exposures to various chemical agents, DOD refers to an allocation of slightly more than \$15 million for this purpose and describes the process that would be followed to obligate these funds to specific research projects. However, its comments on our recommendation provide no detail on its progress in distributing these funds. In its final report, PAC noted that, "DOD's intransigence in refusing to fund [research on possible long-term health consequences of low-level exposure to chemical warfare agents] until summer 1996 has done veterans and the public a disservice."

8. DOD partially concurs with our recommendation that it refine current approaches of the clinical and research programs for diagnosis of PTSD, consistent with recent IOM suggestions. IOM recently found that, "In view of potential exposure to low levels of nerve agents, certain refinements in the CCEP would increase its value." IOM recommended improved documentation of the screening used during Phase I for patients with psychological conditions such as depression and PTSD, noting that "if there are long-term health effects of nerve agent exposure, it is possible that these effects could be manifested as changes in mood or behavior." IOM has made other specific recommendations that are consistent with our

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**Appendix V**  
**Comments From the Department of Defense**

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findings, including the recommendation that physicians take more complete patient histories regarding the onset of health problems and occupational and environmental exposures to rule out alternative explanations for neuropsychological findings.<sup>53</sup> In its comments, DOD refers to diagnostic procedures used in Phase II of the CCEP examination, but these cover a small proportion of participants.

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<sup>53</sup>See Institute of Medicine, *Adequacy of Comprehensive Clinical Evaluation Program: Nerve Agents* (Washington, D.C.: National Academy Press, 1997), pp. 16-17.

# Comments From the Department of Veterans Affairs

Note: GAO comments supplementing those in the report text appear at the end of this appendix.



THE SECRETARY OF VETERANS AFFAIRS  
WASHINGTON

JUN 17 1997

Mr. Kwai-Cheung Chan  
Director, Special Studies and Evaluation  
National Security and International Affairs Division  
U. S. General Accounting Office  
441 G Street, NW  
Washington, DC 20548

Dear Mr. Chan:

I have received your draft report, *PERSIAN GULF WAR ILLNESS: Improved Monitoring of Clinical Progress and Re-Examination of Research Emphasis Needed* (GAO/NSIAD-97-163) and am eager to provide these comments.

Overall, the Department of Veterans Affairs does not concur with the report's conclusions and recommendations. Indeed, the very title alludes to the popular misconception that there exists a single "Persian Gulf War Illness" when in fact, the health problems our veterans are experiencing are many, varied, and often perplexingly unconnected. Furthermore, we believe the report's recommendations reflect a lack of understanding of clinical research, epidemiology, and toxicology. However, there are some aspects of the report that we believe have merit. But even in the specific instances where we agree with GAO, VA had already taken appropriate actions, prior to our receipt of this report.

I consider sound, effective, scientific research to be a key solution in the resolution of the many unexplained health issues surrounding our Persian Gulf War Veterans. To this end, I am committed to supporting and adhering to the strictest of research standards to address these many questions.



Putting Veterans First

See comment 1.

Appendix VI  
Comments From the Department of  
Veterans Affairs

2.

Mr. Kwai-Cheung Chan

I appreciate the opportunity to provide these comments. VA takes GAO's efforts to provide input on our programs and processes quite seriously, and this is a particularly important draft report. Given our strong interest in this subject, and our desire for full and accurate representations of the facts, I am providing copies of these comments to Senate Committee on Armed Services Chairman Strom Thurmond and House Committee on National Security Chairman Floyd Spence.

Sincerely yours,



Jesse Brown

JB:vz

Enclosure

DEPARTMENT OF VETERANS AFFAIRS  
COMMENTS TO THE GENERAL ACCOUNTING OFFICE REPORT:

*GULF WAR ILLNESS: Improved Monitoring of Clinical Progress  
and Re-Examination of Research Emphasis Needed*  
(GAO/NSIAD-97-163)

**General**

The General Accounting Office (GAO) report: "Gulf War Illness" was the result of an evaluation by staff of the GAO Division of National Security and International Affairs of:

- (1) Department of Defense (DoD) and Department of Veterans Affairs (VA) efforts to assess the quality of treatment and diagnostic services provided to Gulf War veterans;
- (2) The government's research strategy to study the veterans' illnesses and the methodological problems posed in its studies; and
- (3) The consistency of key official conclusions with available data on the causes of veterans' illnesses.

GAO concludes that:

- (1) Neither DoD nor VA has systematically attempted to determine whether ill Gulf War veterans are any better or worse today than when they were first examined;
- (2) The ongoing epidemiological research will not be able to provide precise, accurate, and conclusive answers regarding the causes of veterans' illnesses because of formidable methodological problems; and
- (3) The evidence to support several conclusions of the Presidential Advisory Committee on Gulf War Veterans' Illnesses is questionable.

GAO recommends that:

- (1) DoD and VA develop and implement a plan, including the establishment of a centralized database, to monitor the clinical progress of veterans in order to identify appropriate and effective treatment and provide direction to the research agenda;
- (2) DoD and VA give greater priority to research on treatment for ill veterans and on low-level exposures to chemicals and their interactive effects and less priority to further epidemiological studies;
- (3) The Secretaries of Defense and Veterans Affairs refine the current approaches of the clinical and research programs for diagnosing post-traumatic stress disorder.



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VA generally does not concur with the recommendations of the GAO report. The report reflects a lack of understanding of clinical research, epidemiology, and toxicology. The conceptual processes by which GAO reached its conclusions are neither scientifically sound nor logical, and they are internally inconsistent. It also appears that these conclusions reflect an incomplete collection of information. However, there are selected aspects of the report that VA acknowledges as having merit. Indeed, in the specific instances where VA agrees with GAO, appropriate actions had already been undertaken by VA prior to receipt of this report.

VA's responses will generally be directed at the GAO recommendations. Following this, we provide specific comments about statements in the report that are inaccurate, contain factual errors, or are unsubstantiated.

**General Responses to Recommendations**

**Recommendation 1:**

DoD and VA (should) develop and implement a plan, including the establishment of a centralized database, to monitor the clinical progress of veterans in order to identify appropriate and effective treatment and provide direction to the research agenda.

**VA Response:**

VA does not concur with this recommendation. National clinical databases currently exist for the VA Persian Gulf Registry Health Examination, the outpatient care and the inpatient (Patient Treatment File) databases. None of the existing databases are appropriate tools to provide an accurate and valid assessment of the natural history of disease or effectiveness of therapies in Gulf War veterans, nor is establishment of a new database likely to provide satisfactory answers to the question posed by this recommendation.

The clinical programs for Persian Gulf veterans (the VA Registry Program and the DoD Comprehensive Clinical Evaluation Program (CCEP)) have been judged to be of high quality, equal to or exceeding standards within the non-VA civilian community. Both the National Academy of Sciences' Institute of Medicine (IOM) and the Presidential Advisory Committee (PAC) have recently published reports which support the use of the existing clinical protocol. IOM2 (IOM 1996a) and the PAC (PAC, 1997) recommended DoD on their clinical approaches to Persian Gulf veterans' illnesses. The IOM2 report states: "The CCEP is a compassionate and comprehensive effort to address the clinical needs of thousands of active-duty personnel who served in the Persian Gulf War. The CCEP clinical protocol is a thorough, systematic approach to the diagnosis of a wide spectrum of diseases." It should be pointed out that the VA Registry and DoD protocol are nearly identical. The PAC report "concurs with the Institute of Medicine's conclusion that the clinical evaluation programs of the Department of Defense (DoD) and VA are excellent for the diagnosis of Gulf War veterans' illnesses." VA and DoD are committed to providing quality health care and special diagnostic programs to Gulf War veterans,

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and as evidence of this commitment, each Department has contracted with the IOM to provide further clinical program review.

The GAO recommends that "a centralized database, to monitor the clinical progress of veterans be established to identify appropriate and effective treatment." The GAO points to the lack of a systematic approach to treatment after the initial clinical diagnostic evaluations, but fails to address the inherent problems involved in monitoring health outcomes in the absence of a single, well-defined illness. Numerous expert oversight and advisory groups have concluded that the illnesses of Gulf War veterans do not represent a single or unique diagnostic entity, but span the entire range of diagnostic categories of illness. Appropriateness and effectiveness of treatment can only be determined for a specific medical condition whose pathogenesis and natural history has been well characterized. If the purpose of establishing a centralized database is to monitor the clinical progress of veterans, the questions must be asked: Progress for what medical condition? How is clinical progress to be measured? Against what scientific standard should the clinical outcomes of Gulf War veterans be compared?

The goal of research on Persian Gulf veterans' illnesses is, as stated in both editions of *A Working Plan for Research on Persian Gulf Veterans' Illnesses* (PGVCB, 1995, 1996), to determine appropriate diagnostic, therapeutic, and prevention measures. The scientific community is unanimous that to systematically evaluate the effectiveness of medical treatments a research study must be conducted. The gold standard of research to measure outcomes of a treatment is a randomized clinical trial (RCT). An RCT requires a clear disease definition, a clearly defined and measurable outcome, and a medically plausible and scientifically sound treatment which is administered according to an exacting and standardized protocol, and that the intervention be compared to an alternate treatment provided to the control group. These requirements can not be satisfied at the current time for the entire group of Gulf War veterans.

However, the absence of a single unifying case definition that uniquely describes Persian Gulf veterans' illnesses does not mean that Persian Gulf veterans are not provided accepted treatments for their illnesses. The majority of Persian Gulf veterans receive diagnoses and are treated for the diagnosed conditions. Those veterans who receive no diagnosis for their illnesses (which only amounts to 10-25% of the veterans on the VA Persian Gulf Registry) are treated appropriately for their symptoms. This situation is not unlike the experience of civilian primary care practice. The treatments provided to veterans and the management of their medical conditions follow the community standard of modern health care practices. We believe that they serve the Gulf War veterans well.

After discussions with GAO staff, we believe GAO arrived at this recommendation based on suggestions put forward by IOM2 in its report (IOM, 1996a) in which it suggested that the CCEP could be used for several purposes including: (1) education of Persian Gulf veterans and the physicians caring for them; (2) improvement of the CCEP itself; (3) evaluation of patient outcomes. However, unlike the recommendation put forward by the GAO in this report, the IOM2 panel was more

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specific and restrictive in its recommendation. Recognizing that most health registries are not research tools, IOM2 elaborated on the third suggestion further. It said that "The most common diseases in the CCEP could be identified, and suggested approaches to patient treatment could be developed." This is very different from the GAO recommendation. The IOM2 is recommending, in effect, that the registries be used as health surveillance tools to describe the characteristics of this self-selected population and generate hypotheses for future research.

Longitudinal studies of Gulf War veterans with specific diagnoses could be of value. Indeed, VA was first to embark on such a study related to psychological outcomes in all veterans who returned from the Persian Gulf through Ft. Devens. Researchers at Boston VA Medical Center provided health questionnaires to veterans as they were processed through Ft. Devens on their return home from the Persian Gulf. These veterans have been re-studied on two subsequent occasions, the most recent as a part of the Boston VA Medical Center Environmental Hazards Research Center. The PGVCB has recognized the need and importance of more longitudinal research. The revised *Working Plan for Research on Persian Gulf Veterans' Illnesses*, published in late 1996, recommends more longitudinal studies among its list of research recommendations. However, caution must be exercised even in carrying out this recommendation. Any longitudinal study of Persian Gulf veterans must be carefully designed with an appropriate group for comparison of outcomes, otherwise confounding factors may negate the validity of the study.

VA believes that the Persian Gulf Veterans Coordinating Board, through the Research Working Group, is approaching research in an appropriate strategic manner. The epidemiological studies are designed to estimate disease and illness prevalence and define risk factors. These approaches are well recognized by clinical epidemiologists as being essential in a stepwise approach toward the determination of appropriate treatment strategies. Indeed, IOM2 states in its report (IOM, 1996a) that "The DoD and DVA are performing or funding several epidemiological studies that may have implications for CCEP patients and their physicians. These include (1) studies focusing on exposure assessment and (2) studies focusing on health conditions among Persian Gulf veterans. The results of these studies may be useful for making revisions or improvements in the CCEP medical protocol itself..."

**Recommendation 2:**

DoD and VA (should) give greater priority to research on treatment for ill veterans and on low-level exposures to chemicals and their interactive effects and less priority to further epidemiological studies.

**VA Response:**

VA partially concurs with this recommendation. VA does not agree with the GAO recommendation that treatment trials for "Gulf War Illness" should be carried out. VA finds that the second half of the recommendation reflects a misunderstanding of the

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PGVCB research recommendations contained in the original and revised *Working Plan for Research on Persian Gulf Veterans' Illnesses* (PGVCB, 1995 and 1996).

The majority of VA Registry participants have conventional medical diagnoses and are being treated with appropriate therapies according to the best practices of the established medical community. The remaining group of VA Registry participants with unexplained symptoms cannot be subjected to clinical treatment trials in the absence of an accepted case definition or clearly defined condition. Medical experts have agreed that the undiagnosed conditions of Gulf War veterans do not represent a single entity - even among this subgroup of veterans the illnesses appear to be heterogeneous. Treatment trials with poorly defined case definitions would not lead to replicable or definitive conclusions, and have the potential to be viewed as unethical.

However, VA does agree that well-designed clinical treatment trials on individual disease entities which are shown to occur at high frequency in the Gulf War population could be valuable, if those conditions are characterized by a clear case definition. The descriptive epidemiology studies now underway and near completion may help identify such conditions for future study.

With respect to the suggestion that we give greater priority to research on low-level exposures to chemicals and their interactive effects, VA and DoD, through the PGVCB, had already implemented such an increased effort. The investment in research on the health effects of low-level exposures was increased by DoD to \$15 million. This process began in July 1996, well before the GAO report. Early in the establishment of the research agenda, VA (and the PGVCB) chose not to address chemical warfare agent exposure as a specific risk factor. It did this because it was vital to prioritize research and focus on those areas that looked most promising. As part of its prioritization efforts, the PGVCB took seriously recommendations from DSB and IOM2 that pursuit of chemical and biological warfare agents would not be a fruitful avenue of approach because of the lack of evidence for use of or general exposure to these agents. However, as a result of events at Khamisiyah, VA (through the PGVCB) reordered its priorities to invigorate its research portfolio with additional research on the health effects of low-level chemical warfare agent exposure. From the outset, the research portfolio has emphasized investigation of outcomes that would be related to a wide range of alleged exposures, including neurotoxins. In particular, clinical research has focused considerable effort on neurological and neurobehavioral outcomes that could be associated with a number of exposures including pesticides, solvents, chemical warfare nerve agents, and pyridostigmine bromide.

The recommendation that VA and DoD give less priority to epidemiological research is one with which VA and the PGVCB can only partially agree. Indeed, this is a direction that has been followed by the government research efforts for the past year. However, it would not have been appropriate to take this approach earlier in the research strategy. Early on, it was of key importance to do well-designed epidemiology studies to determine the prevalence of symptoms and medical conditions in Gulf War veterans.

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Therefore, in the first edition of *A Working Plan for Research on Persian Gulf Veterans' Illnesses* (PGVCB, 1995), the recommendations for further research focused on epidemiological approaches and the pressing need to assess disease prevalence and to evaluate the severity and general nature of illnesses and disease. These recommendations focused on mortality, general health, and birth outcomes. VA has recognized that our current investment in epidemiological research should not be indiscriminately expanded at this time. However, epidemiologic research to explore new knowledge and hypotheses uncovered by early studies must be pursued. Some examples of this research includes continuation of the mortality study and examination of the increased rate of accidental deaths in Gulf War veterans, further studies of reproductive outcomes in Gulf War veterans, and examinations related to the health of veterans potentially exposed to chemical warfare agents.

This partial shift of emphasis is already evident in the recommendations of the updated *A Working Plan for Research on Persian Gulf Veterans' Illnesses* (PGVCB, 1996b). The recommendations in the latter document stress toxicological research, in particular on chemical warfare agents, and appropriate epidemiological follow-up for specific endpoints such as mortality.

VA strongly disagrees, though, with assertions contained within the GAO report that the epidemiological research to date has been inappropriate and is not likely to yield definitive conclusions. We would also like to point out that basic research alone will also fail to reach the high cause and effect standard set by GAO for Gulf War veterans illnesses. Animal toxicological studies, though useful in understanding mechanisms of toxicity, are severely limited because of problems related to: extrapolation of animal to human experience, comparison of differing exposure routes, and distinguishing responses at different doses. The pursuit of epidemiological research has led to some of the most important findings and conclusions regarding Persian Gulf veterans' illnesses to date. Epidemiological studies have shown so far that: (1) Persian Gulf veterans have not experienced a higher disease-specific mortality rate in comparison to their non-deployed counterparts; (2) Persian Gulf veterans in the military have not been hospitalized more than their non-deployed counterparts; (3) Based on a study of military hospitalization records, birth outcomes among spouses of Persian Gulf veterans and among female Persian Gulf veterans are no different than among their non-deployed counterparts; (4) Persian Gulf veterans are experiencing a greater prevalence of self-reported symptoms. The first three findings were all reported in the *New England Journal of Medicine*, one of the most prestigious peer-reviewed medical journals in the world. The latter findings have been published in a variety of highly respected peer-reviewed publications including the *Journal of the American Medical Association*. Were it not for these epidemiological studies we would still lack answers to vital questions about Gulf War veterans' illnesses. In addition, these studies constitute the most appropriate method to track the health of the Gulf War veteran population and the validity of their results relies on sound epidemiological methods.

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**Recommendation 3:**

The Secretaries of Defense and Veterans Affairs refine the current approaches of the clinical and research programs for diagnosing post-traumatic stress disorder.

**VA Response:**

VA does not concur with the GAO recommendation. VA strongly agrees that PTSD is an important issue for veteran populations. However, VA is currently a recognized leader in the scientific community regarding its approach to clinical care and research in post-traumatic stress disorder. VA has a large, broad-based PTSD research program, a sexual trauma treatment program, a National Center for PTSD, and a health care system with an excellent ability to care for veterans suffering from PTSD. In addition, a significant investment is already underway to enhance our health care and scientific investigations related to PTSD.

Because of VA's concern about the relationship between stress and various health outcomes (including PTSD), VA and DoD are investing an additional \$5 million in research on stress and stress-related disorders. We believe that the results of this research will further improve our clinical approaches to PTSD and other stress-related disorders. In addition, VA is supporting a new multi-center treatment trial for PTSD, as well as a multi-center trial of the diagnostic utility of a computerized neuropsychiatric test battery that should help distinguish psychiatric problems from neurological problems. VA will soon be soliciting additional treatment research on PTSD.

Lastly, it should be pointed out that in their investigations of the PTSD issues, the GAO failed to visit the VA National Center for PTSD or the Environmental Hazards Research Centers at Boston VAMC which is staffed by internationally known PTSD experts. We feel that the discussion of PTSD reflects a superficial understanding of PTSD research and clinical issues.

**Specific Comments on Other Points**

**VA COMMENT ON TITLE OF THE GAO REPORT:**

The overall message of the GAO report is that there is a single Gulf War Illness for which an optimal treatment can be devised. We disagree with the title of this report and the erroneous message that the report itself conveys. A unique "Gulf War Illness" has not been identified. Based on current clinical information and research data, as well as the published findings and conclusions of several panels of distinguished scientists and clinicians (National Institutes of Health (NIH), Defense Science Board (DSB), two Institute of Medicine (IOM1, The Health Consequences of Service in the Persian Gulf War; IOM2, Evaluation of the Department of Defense Comprehensive Clinical Assessment Program) panels, the Presidential Advisory Committee on Gulf War Veterans' Illnesses (PAC)), Gulf War veterans appear to be suffering from multiple conditions with overlapping symptoms. While these findings are not yet considered

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definitive, the growing body of rigorous scientific studies to date have supported this conclusion. Throughout this report the GAO dismisses the conclusions of nationally recognized scientists and substitutes poorly supported and referenced, often conflicting conclusions of their own.

**VA COMMENT ON GAO STATEMENT THAT DOD AND VA HAVE NO SYSTEMATIC APPROACH TO MONITORING VETERANS HEALTH AFTER INITIAL EVALUATION AND EFFORTS TO ENSURE QUALITY AND MEASURE SATISFACTION WITH INITIAL EXAMINATIONS ARE NOT ADEQUATE**

See comment 6.

VA has developed a successful national approach to quality management in its health care system. It has fully developed programs in quality management, utilization management, risk management and customer satisfaction. Its programs reach or exceed the standards found in the civilian health care system and monitor health care quality and appropriateness for all veterans, including Gulf War veterans.

This GAO recommendation reflects a lack of understanding concerning the nature of Gulf War veterans' illnesses. Currently, there is no evidence of a single unifying illness to explain the health problems of all Gulf War veterans. The lack of a single diagnosis and the heterogeneous nature of the unexplained illnesses make monitoring the "quality, appropriateness, or effectiveness of care provided to Gulf War veterans" after Registry examinations a significant challenge.

GAO acknowledges that VA has a quality monitor for Registry programs. They fail to acknowledge the reported improvements in performance as measured by this instrument since its implementation in 1995. The results of the self-assessment/quality management monitor for the Registry health examination are compiled nationally and returned to each VAMC for comparison of local with national results. The newly established SEAT program will use the data obtained from this monitor in its activities. In March 1997, VHA established Service Evaluation and Action Teams (SEAT) in all 22 Veterans Integrated Service Network offices. The SEATs were established to monitor quality of care and patient satisfaction with Gulf War veterans programs within each Network. The SEATs will collect data from the self-assessment survey, quality management programs, the patient representative complaint tracking system, helpline referrals, correspondence, and customer satisfaction surveys, in addition to other information sources. We feel that this new activity will enhance our efforts to assure quality health care for Gulf War veterans. The GAO report does not acknowledge these efforts.

On page 29, GAO also acknowledges that VA carries out an annual National Customer Satisfaction Survey. They are correct in stating that the 1996 survey lacked the statistical power to allow valid conclusions regarding the satisfaction of Gulf War veterans compared to their contemporaries who used VA health care services. This was

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related to the small number of Gulf War veterans participating in the survey. However, GAO fails to record the efforts which began in Fall 1996 to adapt the 1997 survey and oversample Gulf War veterans to correct this weakness. We will be able to adequately assess the satisfaction of Gulf War veterans with VA health care through the 1997 survey. Regrettably GAO's omission of VA's progress in expanding its Patient Satisfaction Survey to address Persian Gulf War veteran issues will lead the uninformed reader to an erroneous impression of VA's efforts.

See comment 7.

**VA COMMENT ON GAO STATEMENT REGARDING INABILITY OF  
ONGOING EPIDEMIOLOGICAL RESEARCH TO PROVIDE PRECISE,  
ACCURATE, AND CONCLUSIVE ANSWERS REGARDING THE CAUSES OF  
VETERANS' ILLNESSES BECAUSE OF FORMIDABLE METHODOLOGICAL  
PROBLEMS:**

The GAO report asserts that "Because of formidable methodological problems facing investigators, research on Gulf War veterans' illnesses will not be able to provide precise, accurate, and conclusive answers regarding the causes of veterans' illnesses". While VA agrees that GAO has identified the greatest challenge that Gulf War researchers face -- that is the lack of objective measure of exposure -- we disagree that epidemiologic research is unable to provide valid and important information about the health consequences of Gulf War service. This GAO statement is not consistent with accepted clinical and research principles. The current epidemiologic research portfolio has provided and will continue to provide valuable information on the health of Gulf War veterans and their families. The ongoing research will clarify prevalence, natural history, and risk factors for illnesses associated with Persian Gulf War service. We agree that it is indeed possible that a Gulf War-related exposure may never be precisely linked to Gulf War veterans' illnesses (regardless of how well a study may be designed or what type of research is conducted), but the importance of discovering the possible health outcomes associated with Gulf War service, even in the absence of causal inference should not be so casually dismissed.

The GAO suggests that the only valuable exposure data is objectively measured, quantitative data on the exposure to pesticides, oil well fires, etc. While these exposure measures would be optimal, there are additional exposure surrogates that can potentially be valuable and enlightening. For example, exposure variables can include the dates and duration of service in the Gulf, the location of deployment in the Persian Gulf, and military occupation during the Gulf War. Epidemiological studies are currently acquiring these types of data.

**VA COMMENT ON GAO CRITICISM OF THE PRESIDENTIAL ADVISORY  
COMMITTEE ON GULF WAR VETERANS' ILLNESSES:**

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See comment 8.

The GAO report contradicts some of the most important findings and recommendations of every outside expert panel that has been assembled to advise the executive branch of the federal government on clinical and research matters relating to Persian Gulf veterans' illnesses. Using a small staff, GAO spent less than six months studying Persian Gulf veterans' illnesses. In contrast, the IOM1 panel spent nearly 3 years, and the PAC spent 18 months on its investigations. Each of these panels was composed of renowned scientists (with multidisciplinary expertise including , epidemiologists, toxicologists, biostatisticians, and clinical researchers). Membership on the PAC was likewise highly distinguished including current or past academic deans, department heads or equivalent, a former Chief Medical Director of the Department of Veterans Affairs, and the President of the Carnegie Foundation, who also has been President of the Institute of Medicine, and of the American Association for the Advancement of Science. The findings, conclusions, and recommendations in their reports are supported by hundreds of references (209 in the IOM1 report and 343 in the PAC report) as well as testimony of and interviews with numerous renowned scientists, who provided independent assessments of the health outcomes and exposures frequently associated with Persian Gulf veterans' illnesses. In comparison with these efforts, the GAO report is thinly supported with few references (approximately 35). Furthermore, there is no evidence that GAO sought independent expert advice either during the report preparation phase or after the preparation of the draft report. The IOM1 and IOM2 reports, besides being produced by distinguished panels, were peer-reviewed and received critical comment by a second panel of outside experts selected by the IOM prior to final report publication.

See comment 9.

See comment 10.

The GAO report implies that VA and DoD have taken inappropriate clinical and research approaches to Persian Gulf veterans' illnesses in part because the Departments have used the best expert advice from government and non-government experts and have given due weight to the recommendations of outside review panels (such as IOM1, IOM2, and PAC). Because of their commitment to providing the best health care for Persian Gulf veterans, as well as the best research, VA and DoD have continuously sought outside opinions of experts. We are committed to pursuing the best responses to the health problems of Gulf War veterans and continually improving our clinical and research strategies. The best means to reach our goals to optimize clinical programs and enhance research approaches, is to seek independent expert advice and reviews. Indeed, outside peer review has been frequently cited by Congress as the best way to ensure that federally-supported science is well conducted. This report suggests that the process of outside peer review has either been ineffective or is flawed. We disagree.

**VA COMMENT ON GAO STATEMENT THAT EXECUTIVE BRANCH  
AGENCIES WERE SLOW IN RESPONDING TO GULF WAR VETERANS'  
HEALTH CONCERNS:**

This inaccurate statement denies and, in fact, undermines the early and comprehensive efforts the agencies have pursued. The VA Registry Health Examination

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Program was designed in 1991 and implemented in 1992. The VA Persian Gulf Referral Centers were initiated in 1992. VA supported, and Congress passed, priority care for Persian Gulf War veterans whose health conditions are potentially related to an environmental or hazardous exposure that occurred during Gulf War service. Since 1991, VA has provided 1.8 million outpatient visits to more than 191,000 Gulf War veterans; 33,000 VAMC hospitalization to more than 19,000 veterans; more than 66,000 Registry examinations have been completed and more than 74,000 veterans have received services at Vet Centers nationwide. The history of VA's health care response to the concerns and needs of Gulf War veterans negates the GAO's statement.

Furthermore, the GAO asserts that "...the vast majority of research was not initiated until 1994 or later." Both of these statements are inaccurate. VA and DoD were highly proactive regarding potential health problems of Persian Gulf veterans both during and after the cessation of hostilities in the Persian Gulf. In April 1991, at a time when no veterans had expressed concern about their health, VA proactively embarked on the Persian Gulf Registry program. This and the other events that followed such as the investigation of the outbreak of illnesses at the 123<sup>rd</sup> ARCOM in Indiana were prudent clinical responses to what, at that time, was clearly not a subject for a major research program.

Research that had been initiated by VA investigators soon after the end of the Persian Gulf War (such as the Fort Devens Reunion Study initiated by the Boston VA Medical Center) was appropriately directed to take immediate advantage of opportunities to study the health effects associated with deployment and combat in Persian Gulf veterans.

When the oil well fires were ignited during the ground war, the US Environmental Protection Agency led the formation of an Interagency Air Assessment Team (USIAAT) composed of scientists from EPA, HHS(CDC), DOE, and DOC. The USIAAT was dispatched to the Persian Gulf in early March 1991, within days of the end of hostilities, to assess the potential health impacts of the oil well fires on US troops, citizens, and indigenous populations. A preliminary report of findings was issued in April 1991 (US EPA, 1991). The USIAAT helped the US Army Environmental Hygiene Agency launch their oil well fire assessments in May, 1991. In late 1991, EPA prepared a more detailed report that incorporated results and findings of approximately 10 other efforts by domestic and foreign entities to evaluate the health impacts of the oil well fires. In 1992, GAO evaluated the USIAAT and DoD efforts regarding the oil well fires (GAO, 1992a,b) and found them to be appropriate.

One of the research efforts that the present GAO report asserts started in 1994 was establishment of the three VA Environmental Hazards Research Centers. Although the Centers began their work in 1994, the selection of these Centers was the culmination of a request for proposals issued in 1993. Prior to that solicitation and in addition to the established investigator-initiated research that was already ongoing in VA, the Office of Research and Development established three pilot research programs to address emerging

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health concerns of Persian Gulf veterans, including issues related to potential environmental factors. Because it was recognized that research takes time, VA, DoD, and HHS solicited in 1993 the advice of internationally renowned scientists to evaluate the then existent knowledge of Persian Gulf veterans' illnesses and the potential risk factors. The Defense Science Board (DSB, 1994) and the Institute of Medicine (IOM, 1996) initiated their investigations in 1993. The National Institutes of Health Technology Assessment panel conducted its work in 1994 (NIH, 1994). Overall, the clinical and research efforts of the Executive Branch of the US government from 1991-1994 were proactive and reflected its concern for the health and welfare of Persian Gulf veterans.

**VA COMMENT ON GAO STATEMENT THAT SOME HYPOTHESES (FOR EXAMPLE, THAT VETERANS' CURRENT SYMPTOMS ARE DUE TO STRESS) WERE PURSUED MORE AGGRESSIVELY THAN OTHERS:**

The earliest research on Persian Gulf veterans preceded general reports of health complaints among Persian Gulf veterans. For example, the Ft. Devens Reunion Study conducted by researchers at the Boston VA Medical Center (VAMC) sought to ascertain the psychological sequelae of deployment and combat as soon after return to the US as possible. The Vietnam experience taught us much about the psychological effects of war on soldiers, however much of this knowledge was garnered years after the cessation of US involvement in Vietnam. The early efforts to examine the effects at war-related stress were, in fact, not directed at any wide-ranging health complaints of veterans but was a valuable, aggressive, and proactive response on the part of scientists to address a problem that has plagued veterans of past wars. Furthermore, these research efforts were not centrally directed by VA, but were the result of investigators' own initiative.

It should be pointed out that VA highly values investigator-initiated research because it is guided by the clinicians that are the most expert in understanding health problems associated with military service. Furthermore, by 1994 the research investments of VA covered virtually every potentially important risk factor known then and now, including the effects of exposure to organophosphate (OP) pesticides and nerve agents.

The reference in the GAO report to "an example" of privately funded research on OP pesticides is, in point of fact, only one of two privately funded research efforts that we know of. The referenced research was conducted by Dr. Mohammed Abou-Donia of Duke University and Dr. Robert Haley of the University of Texas Southwest Medical Center. Both of these investigators were supported by the Ross Perot foundation, and the research products from these studies (Abou-Donia et al, 1996 and Haley et al 1997a,b,c), though important, are of limited value in our ongoing efforts to understand Persian Gulf veterans' illnesses (PGVCB, 1997). The other privately funded research is that of a British scientist (Jamal et al, 1996), the results of which are also of questionable value.

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**VA COMMENT ON GAO STATEMENT THAT POPULATION-BASED COMPARISONS THAT GROUP TOGETHER VETERANS WITH VARIED EXPOSURES MAY MASK STATISTICALLY SIGNIFICANT DIFFERENCES IN ILLNESS RATES AMONG SUBGROUPS OF VETERANS:**

This would be true if there were no attempts to stratify within groups, which are planned for many of the investigations. Secondary analyses of population-based studies involving stratification are vitally important aspects of these investigations and they will be carried out.

**VA COMMENT ON GAO STATEMENT THAT THE LINK BETWEEN STRESS AND THESE VETERANS' PHYSICAL SYMPTOMS IS NOT WELL ESTABLISHED, AND THE REPORTED PREVALENCE OF POST-TRAUMATIC STRESS DISORDER (PTSD) AMONG GULF WAR VETERANS MAY BE OVERESTIMATED:**

Studies exploring the link between exposure to stress and health outcomes in Persian Gulf veterans is subject of ongoing research. There have been no conclusions made by the government (including the Presidential Advisory Committee) asserting that stress is THE CAUSE of Persian Gulf veterans' illnesses. While, the link between exposure to stress and adverse health sequelae is well established in the scientific literature, much additional research is needed to better understand the biological mechanisms responsible for this relationship and to ascertain whether these findings are relevant to the health outcomes of Gulf War veterans. To suggest that such a link has not been established is to contradict decades of research in this area.

The suggestion by GAO that the prevalence of PTSD may be overestimated in Gulf War veterans is unsubstantiated. Indeed, research on PTSD in Persian Gulf veterans shows that generally the rates are relatively low, and that elevations in rates are dose-dependent, i.e. those groups of veterans with greater exposure to human carnage or violent behavior, whether in combat or as a result of sexual abuse, had higher rates of PTSD. This is acknowledged in the recent Annual Report to Congress (PGVCB, 1997), the revised Working Plan for Research on Persian Gulf Veterans' Illnesses (PGVCB, 1996b), and the final report of the Presidential Advisory Committee on Gulf War Veterans' Illnesses (PAC, 1997).

**VA COMMENT ON GAO STATEMENT ABOUT THE NEED TO RETAIN LEISHMANIASIS AMONG THE POTENTIAL RISK FACTORS:**

VA and DoD have not dismissed Leishmaniasis as a potential risk factor for Persian Gulf veterans' illnesses. However, only 12 documented cases of viscerotropic leishmaniasis among Gulf War veterans exist despite extensive efforts to identify additional cases. The absence of new cases strongly suggests that this is not a likely

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explanation for the illnesses of Gulf War veterans. Research efforts to identify a better serologic test for Leishmaniasis are supported by the PGVCB and are ongoing. If these efforts are successful, a seroepidemiologic study could be carried out to better assess the potential contribution of leishmaniasis to Gulf War veterans' illnesses.

**VA COMMENT ON GAO STATEMENT THAT SUBSTANTIAL EVIDENCE THAT SUCH COMPOUNDS [ORGANOPHOSPHATES (OP), INCLUDING CHEMICAL WARFARE NERVE AGENTS] ARE ASSOCIATED WITH DELAYED OR LONG-TERM HEALTH EFFECTS SIMILAR TO THOSE EXPERIENCED BY THE GULF WAR VETERANS:**

The health effects referred to by GAO are organophosphate induced delayed peripheral neuropathies (OPIDN). First, there is no clinical evidence from the VA Registry or the DoD CCEP that a large number of Gulf War veterans have been diagnosed with peripheral neuropathies. Second, two research reports (Jamal et al, 1996, and Haley et al, 1997) which purport to demonstrate alterations in the peripheral nervous system of Gulf War veterans do not, in fact, show electrophysiologic abnormalities diagnostic of peripheral neuropathies. Third, although OP pesticides can lead to OPIDN, OP chemical warfare nerve agents alone cannot cause OPIDN because victims of chemical warfare nerve agent exposure would experience the lethal effects of these agents before sufficient doses required to induce a peripheral neuropathy are achieved (NRC, 1983).

However, VA and the PGVCB are concerned about the possibility of other long-term effects of low-level exposure to chemical warfare agents. This has prompted DoD, in conjunction with the PGVCB, to invest an additional \$15 million in research on the health effects of low-level exposure to chemical warfare agents. These funds are over and above the current investments of VA and DoD. Research proposals to address this problem have been scientifically peer-reviewed and are undergoing programmatic review by the Persian Gulf Veterans Coordinating Board to ensure that the most meritorious and most relevant research is funded.

**VA COMMENT ON THE GAO STATEMENT THAT THE HEALTH EFFECTS OF POTENTIAL EXPOSURE TO AFLATOXIN ARE NOT BEING CONSIDERED BY VA AND DOD:**

There is no evidence of acute liver problems occurring during the Persian Gulf war that could be indicative of an exposure to aflatoxin. If the concentrations of aflatoxin were below that expected to cause acute effects, there is a possibility that liver cancer could occur much later (>20 years). VA and DoD have monitored mortality (Kang et al, 1996) and military hospitalizations (Grey et al, 1996) and have found no increases in deaths or hospitalizations due to cancer among Persian Gulf veterans in comparison with their non-deployed counterparts. However, in recognition of the fact that cancers usually

See comment 14.

See comment 15.

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have long latency periods, VA committed itself in its revised *Working Plan for Research on Persian Gulf Veterans' Illnesses* (PGVCB, 1996b) to conducting mortality follow-up studies at appropriate time intervals to allow for the possibility of disease latencies leading to increased mortality in the future.

**VA COMMENT ON THE GAO STATEMENT THAT THE FEDERAL  
RESEARCH STRATEGY LACKS A COHERENT APPROACH:**

The federal research strategy is sound and has been deemed appropriate by both the Institute of Medicine (IOM, 1996b) and the PAC (PAC, 1997). The three goals for research articulated in the original and revised *Working Plan for Research on Persian Gulf Veterans' Illnesses* (PGVCB, 1995 and 1997b) are, briefly: (1) the determination of the prevalence of symptoms, illnesses, and disease; (2) the determination of risk factors; and (3) the development of appropriate diagnostic, treatment, and prevention strategies. The first goal was recognized very early as an important component of a research strategy, for without prevalence data, the ability to carry out the subsequent two goals would be virtually impossible. The need for the first goal was first articulated by the NIH Technology Assessment Workshop panel in 1994 (NIH, 1994).

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REFERENCES – GAO RESPONSE

1. Abou-Donia M, Wilmarth K, Oehme F, Kurt T. Neurotoxicity resulting from coexposure to pyridostigmine bromide, DEET, and permethrin: implications of Gulf War chemical exposure. *J Tox Env Health*; 48:35-36, 1996.
2. DSB (Defense Science Board). Final Report: Defense Science Board Task Force on Persian Gulf War Health Effects. Washington, D.C.: Office of the Under Secretary of Defense for Acquisition and Technology, 1994.
3. EPA (Environmental Protection Agency). Kuwait Oil Fires: Intragency Interim Report. Washington, DC, 1991.
4. GAO (United States General Accounting Office). Report on Defense Health Care: Efforts to Address Health Effects of the Kuwaiti Oil Well Fires. Washington, D.C.: GAO/HRD-92-50. January 1992.
5. GAO (United States General Accounting Office). Report on International Environment: Kuwaiti Oil Fires Chronic Health Risks Unknown but Assessments Are Under Way. Washington, D.C.: GAO/RCED-92-80BR. January 1992.
6. Gray GC, Coate BD, Anderson CM, Kang HK, Berg SW, Wignall FS, Knoke JD, Baret-Connor E. The postwar hospitalization experience of US Persian Gulf War veterans. *New England Journal of Medicine* 1996; 335:1505-13.
7. Haley RW, Kurt TL, Hom J. Is there a Persian Gulf syndrome? Searching for syndromes by factor analysis of symptoms. *JAMA*; 277:215-22, 1997.
8. Haley, RW, Hom J, et al. Evaluation of neurological function in Gulf War veterans. *JAMA*; 277:223-30, 1997.
9. Haley RW, Kurt TL. Self-reported exposure to neurotoxic chemical combinations in the Gulf War. *JAMA*; 277:231-37, 1997.
10. IOM (Institute of Medicine). Health Consequences of Service During the Persian Gulf War: Initial Findings and Recommendations for Immediate Action. Committee to Review the Health Consequences of Service During the Persian Gulf War. Medical Follow-up Agency; Institute of Medicine. National Academy Press, Washington, DC, 1995.
11. IOM (Institute of Medicine). Health Consequences of Service During the Persian Gulf War: Final Report. Committee to Review the Health Consequences of Service During the Persian Gulf War. Medical Follow-up Agency; Institute of Medicine. National Academy Press, Washington, DC, 1996.
12. Jamal GA, Hansen S, Apartopoulos F, Peden A. The "Gulf War Syndrome": is there evidence of dysfunction in the nervous system? *J Neurology, Neurosurgery and Psychiatry*; 60:449-4512, 1996.
13. Kang, HK, and Bullman, TA (1996). Mortality among U.S. veterans of the Persian Gulf War. *New England Journal of Medicine* 335, 1498-1504.
14. NRC (National Research Council). Possible Long-Term Health Effects of Short-Term Exposure to Chemical Agents. Volume 1: Anticholinesterases and Anticholinergics. National Academy Press, Washington, DC, June 1982.
15. NRC (National Research Council). Possible Long-Term Health Effects of Short-Term Exposure to Chemical Agents. Volume 2: Cholinesterase Reactivators,

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- Psychochemicals, and Irritants and Vesicants. National Academy Press, Washington, DC, 1984.
16. NRC (National Research Council). Possible Long-Term Health Effects of Short-Term Exposure to Chemical Agents. Volume 3: Final Report – Current Health Status of Test Subjects. National Academy Press, Washington, DC, 1985.
  17. NIH (National Institutes of Health Technology Assessment Workshop Panel). The Persian Gulf experience and Health. JAMA; 272(5);391-396, 1994.
  18. PAC (Presidential Advisory Committee on Gulf War Veterans' Illnesses). Final Report. Washington, DC, December 1996.
  19. PGVCB (Persian Gulf Veterans Coordinating Board). Annual Report to Congress: Federally Sponsored Research on Persian Gulf Veterans' Illnesses'. 1995.
  20. PGVCB (Persian Gulf Veterans Coordinating Board). Annual Report to Congress: Federally Sponsored Research on Persian Gulf Veterans' Illnesses' P92421. 1996a.
  21. PGVCB (Persian Gulf Veterans Coordinating Board). Annual Report to Congress: Federally Sponsored Research on Persian Gulf Veterans' Illnesses' IB 10-40. 1996b.
  22. PGVCB (Persian Gulf Veterans Coordinating Board). Annual Report to Congress: Federally Sponsored Research on Persian Gulf Veterans' Illnesses'. 1997.
  23. Wolfe J, Kelley JM, Buscela ML, Mark WR. Ft. Devens Reunion Survey: Report of Phase I. In R. Rosenheck et al. (Eds.). War-zone stress among returning Persian Gulf troops: Final Report. Legislative report to Congress, 1992.

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The following is our response to the Department of Veterans Affairs' letter dated June 17, 1997.

## GAO Comments

1. We have changed the word "illness" in our report title to "illnesses."
2. VA acknowledges that clinical progress cannot be measured with existing or new databases. VA also notes that "appropriateness and effectiveness of treatment can only be determined for a specific medical condition whose pathogenesis and natural history has been well characterized." VA agrees that longitudinal tracking of veterans with specific diagnoses could be of value. The majority of veterans have one or more diagnoses, which, in combination with their chief health complaints, should provide the basis for evaluating their care. Nevertheless, VA emphasizes the difficulty of evaluating the clinical progress of individuals with undiagnosed conditions. We are not suggesting randomized clinical trials of new treatments, as VA appears to imply, but do suggest that the Department develop a plan to monitor the condition of undiagnosed individuals in order to promote effective symptomatic treatment.

Although VA asserts that those veterans who receive no diagnosis for their illnesses are treated appropriately for their symptoms, they do not indicate that they have any means of ensuring this, and they provide no evidence for the assertion. As VA suggests, augmenting its collection of data on the progress of ill Gulf War veterans with additional comparative data would provide valuable additional information. However, at a minimum, it seems desirable to collect descriptive information on how veterans' conditions have improved or worsened.

3. VA agrees that research on low-level exposures to chemicals should be given higher priority but does not believe epidemiological studies should be given lower priority. Since VA does not provide evidence to dispute our findings that ongoing epidemiological studies will not provide accurate, precise, or conclusive answers, we continue to believe that emphasis in the research should be shifted.

4. VA does not concur with our recommendation on the basis that it is already making efforts to refine current approaches of its clinical and diagnostic programs for diagnosing posttraumatic stress disorder (PTSD). The emphasis of our recommendation is not upon how PTSD is diagnosed at specialty centers but upon how it is diagnosed in the course of ordinary registry evaluation and the improved validation of diagnostic methods

used in establishing its prevalence. VA's comments offer no corrective plan. Therefore, we continue to believe that VA should refine the current approaches of the clinical and research programs for diagnosing PTSD.

5. See comment 1.

6. VA's comments do not address our specific finding that it has no information on whether Gulf War veterans are any better or worse today than when they were initially diagnosed. VA suggests that its current approach provides adequate oversight for Gulf War veterans' care. We found that VA relies on quality assurance mechanisms that do not ensure a given level of effectiveness for the care provided. VA agrees with us that the 1996 National Customer Satisfaction Survey was not adequate, and it plans to correct those deficiencies. However, VA has not provided any evidence to us to the contrary. Given the fact that VA has no way to track changes in veterans' health status, we continue to believe that DOD and VA should develop and implement plans to monitor the clinical progress of veterans.

7. While VA agrees that it is indeed possible that a Gulf War-related exposure to agents may never be precisely linked to Gulf War veterans' illnesses (regardless of how well a study may be designed or what type of research is conducted), it believes that epidemiologic research can provide important information about the health consequences of Gulf War service. We agree that descriptive studies cited by VA are useful in understanding group differences, but it is not clear what hypotheses these studies have generated regarding risk factors. Our conclusion remains valid regarding the inability of ongoing epidemiological research to provide precise, accurate, and conclusive answers regarding the causes of veterans' illnesses because of formidable methodological problems.

8. Comments from the Presidential Advisory Committee and our responses are in appendix VII. Our methodology is described on pages 13 and 14 of our report. We use an extensive quality assurance process for all of our products, as we did for this report. The expertise of the team who conducted this review is discussed on page 14.

9. VA notes that our report is thinly supported with few references (approximately 35). However, as we note in our report, we reviewed not only the articles that PAC cited in support of its conclusions (which we do not list) but also articles published in peer-reviewed journals that PAC did not take into consideration (which we do list).

10. Our report does not imply the assertion VA is making. In our evaluation of federal research strategy, we are reporting our findings on the extent to which the strategy is coherent.

11. Our conclusion is based on PGVCB-provided data, which show that the vast majority of federal research was initiated during or after 1994 and relatively few studies have been completed.

12. This is an inaccurate presentation of the statement in our report. We stated in our report that PAC did not provide evidence in support of its assertion that stress is an important contributing factor to the "broad range" of illnesses currently being reported by Gulf War veterans.

13. As our report notes, we reviewed the literature cited by PAC. All but two of these references from peer-reviewed journal articles deal with the putative association with PTSD; only two discuss the role of general life stress. The scientific articles on PTSD do not present convincing evidence that PTSD is common in Gulf War veterans or that it explains the symptoms reported by Gulf War veterans. All but one of the peer-reviewed studies on PTSD in Gulf War veterans relied on psychometric PTSD scales, unaccompanied by psychiatric interviews, and only minimal elevations of scores were found. These do not indicate the presence of PTSD. Virtually any illness that causes primary or secondary emotional concern can produce minimal elevations of scores on the psychometric PTSD scales. The fact that minimal elevations of psychometric scales scores were slightly higher than those of nondeployed veterans proves only that deployed veterans have more illness of some kind, but it does not establish that it is related to PTSD or general life stress.

14. VA failed to understand the central message underlying the two research studies it cited (Jamal et al., 1996, and Haley et al., 1997). These two studies demonstrate that the syndrome of chronic fatigue, cognitive problems, balance disturbances, joint aches, diarrhea, etc., could be neurological injuries from exposure to chemicals in the war. These studies also suggest that routine medical examinations are incapable of detecting chronic neurotoxicity. Thus, the statement that "the majority of VA Registry participants have conventional medical diagnoses and are being treated with appropriate therapies" is undoubtedly sincerely meant and true, but irrelevant.

15. We have stated in our report that while the government found no evidence that biological weapons were deployed during the Gulf War, the

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United States lacked the capability to promptly detect biological agents, and the effect of one agent, aflatoxin, would not be observed for many years.

# Comments From the Presidential Advisory Committee on Gulf War Veterans' Illnesses

Note: PAC's comments on our draft report, along with our responses to these comments, are reproduced here. Due to the length and highly technical nature of PAC's comments, our response follows each individual comment in the letter, rather than at the end of the comments.




Presidential Advisory Committee on Gulf War Veterans' Illnesses

**Chair**  
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**Executive Director**  
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**Deputy Director**  
Gary L. Canuso



June 3, 1997

Mr. Kwai-Cheung Chan  
Director, Special Studies and Evaluation  
National Security and International Affairs Division  
U.S. General Accounting Office  
Washington, DC 20548

Dear Mr. Chan:

Thank you for the opportunity to review the draft GAO report, "Gulf War Illness: Improved Monitoring of Clinical Progress and Re-examination of Research Emphasis Needed." As a familiar reader of GAO documents, I found this draft fell far short of GAO's standards. I regret the blunt directness of the assessment that follows, but the quality of this manuscript is so flawed that no other approach was possible. In its current form the draft is not worthy to stand published along side other GAO efforts.

Given the legislative mandate that GAO analyze the effectiveness of the government's *clinical care* and *medical research* programs relating to Gulf War veterans' illnesses, I am puzzled as to why GAO reviewed the findings of the Presidential Advisory Committee on Gulf War Veterans' Illnesses with respect to *risk factors*, especially as GAO ignored the Committee's review of clinical care and medical research. Moreover, the GAO draft only accounts for the Committee's Final Report, and fails to acknowledge the considerable commentary in the Committee's Interim Report that is relevant to the GAO manuscript. In particular, the Interim Report reviewed in detail the pluses and minuses of the government's epidemiologic major research projects, yet appears to have been ignored by GAO—despite documenting a few similar concerns. These analyses and our review in our Final Report of the government's research (both epidemiologic and toxicologic) should be incorporated, or at least acknowledged, by GAO.

## GAO RESPONSE

The purpose of our evaluation of PAC's conclusions with respect to risk factors was to ascertain the amount of knowledge about Gulf War illnesses generated by research 6 years after the Gulf War, and evaluate the evidence supporting conclusions on these issues. We reviewed these conclusions because they are the strongest statements of any official body that we have found on these matters. Moreover, the PAC review panel included a number of recognized experts in scientific questions at issue who were assisted by a large staff of scientists and attorneys. In addition,

PAC extensively reviewed the research on Gulf War veterans' illnesses. Thus, evaluating the strength of the PAC's conclusions provides important evidence about how fruitful research on Gulf War illnesses has been to date. We have repeated in our letter the statement on this point that we had made in appendix IV.

Our report cites PAC's recommendations and significant conclusions. We also carefully reviewed the PAC's interim report, which cites potential problems for federally funded research. We documented that such problems affect large portions of the federally sponsored studies (see app. III).

I have attempted to limit this review to portions of the draft that directly report on the Committee's work, although I find the broad-based criticisms outlined below applicable to the entire manuscript. Thus, this review principally focuses on finding 3 (page 3): "the evidence to support several conclusions of the Presidential Advisory Committee on Gulf War Veterans' Illnesses is questionable." In some places, however, while the draft text does not explicitly mention the Committee's work, GAO later uses the assertions in critiquing the Committee's conclusions, and so this review encompasses those instances—in particular for finding 2 (page 3) regarding epidemiological research: "the ongoing epidemiological research will not be able to provide precise, accurate, and conclusive answers regarding the causes of veterans' illnesses because of formidable methodological problems." For the most part, this review roughly follows the initial presentation of topics in the GAO draft, with comments to a general subject (e.g., biological warfare agents) made in the context of the first instance, with reference to the appropriate page that has been taken out of sequence. In the interest of space, I do not reiterate in this letter the hundreds of peer-reviewed literature reviewed and cited by the Committee. I do add new citations, as appropriate.

- Factual errors appear throughout the draft; in some instances these inaccuracies further exacerbate the draft's weaknesses. The document does not systematically present an analysis of the topics under consideration. Moreover, it is internally inconsistent in its own analyses. References to scientific literature essentially are non-existent, despite the fact that broad sweeping statements purporting to be based on scientific research occur throughout the draft. When references are cited, they are done so selectively. Finally, the report fails to account for, or even draw upon, the comprehensive work of several independent groups.

#### GAO RESPONSE

Our study is a systematic evaluation of the matters that Congress directed us to examine. We reviewed the scientific literature and published as well as unpublished work of internal and external bodies. In reviewing conclusions, we examined the support cited as well as additional evidence we gathered and compared these with the official conclusions.

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We have added citations to better reflect our use of scientific literature in our review.

- Numbers of studies: On page 4, the draft notes that four-fifths of funded studies are not complete; on page 8 the draft states there are 91 federally sponsored studies, of which 74 were ongoing during GAO's review. As a point of reference, the Committee's Final Report documents 106 federally funded studies, of which 40 are complete, excluding one where major phases are complete, with results reported in the peer-reviewed literature. Nineteen of the studies presented in the Committee's Final Report are not reported on by GAO; the GAO report does list four studies that were funded after the Committee's work was completed.

GAO RESPONSE

As we pointed out in our draft report, the number of studies we cite was taken directly from the most recent (April 1997) annual report to Congress by the official sponsoring and coordinating entity for pertinent research, the Persian Gulf Veterans' Coordinating Board (PGVCB). PGVCB, which coordinates research on Gulf War veterans' illnesses involving VA, DOD, and HHS, is required under Public Law 102-585 to report annually on the results and progress of pertinent research activities undertaken or funded by the executive branch.

- Stress: On pages 5-6 and 11-12, GAO asserts there is weak evidence for the Committee's finding that stress is likely to be an important contributing factor and that studies have found higher rates of posttraumatic stress disorder (PTSD) in Gulf War veterans. First, the Committee notes that stress-related effects are not equivalent to PTSD, yet GAO consistently juxtaposes these two distinct issues and treats them as a single matter—leading GAO to faulty conclusions and to misrepresent the Committee's analysis.

GAO RESPONSE

We do not confuse PTSD and stress-related effects. Indeed, it is unclear how we could both "juxtapose" the distinct issues and simultaneously "treat them as a single matter," as the comment alternately suggests. We address

these items in tandem in order to prevent the very type of misinterpretation about which the Committee is concerned.

In contrast, PAC's report blurs the distinction between PTSD (that is, a specific syndrome caused by emotional trauma) and stress (a potential risk factor). To support its conclusion regarding the contribution of stress to veterans' illnesses, PAC cites 18 reports from peer-reviewed journals, but these largely assess the association between stress and PTSD. Only two peer-reviewed articles were presented in support of the broader effects of stress and neither included measurements of Gulf veterans. Some studies, while intending to assess the extent of PTSD, found little and instead discussed "stress symptomatology," "trauma-related symptoms," or "PTSD symptoms," using these terms to refer to measurements on a PTSD scale that did not meet the validated cutoff for indication of PTSD.

Second, the GAO draft offers no scientific references, in contrast to the Committee's documentation, of the wide range of physical symptoms that can result from stressors. GAO states, "the relationships between stress and veterans' physical illnesses have not yet been established or proven." GAO further states, yet does not reference, "a large-scale, federally funded study concluded that for those veterans who deployed to the Gulf War and currently report physical symptoms, neither stress nor exposure to combat or its aftermath bear much relationship to their distress."

#### GAO RESPONSE

As our report notes, we reviewed the literature PAC cited in support of its conclusion. Only two references from peer-reviewed journals were provided to substantiate the role of general life stress in the etiology of veterans' symptoms.<sup>54</sup> Neither reference presented measurements of Gulf War veterans.

We noted in our report that this quotation is taken from, "R.H. Stretch et al., "Physical Health Symptomatology of Gulf War-era Service Personnel From the States of Pennsylvania and Hawaii," Military Medicine, vol. 160 (1995), pp. 131-36. (See app. II.)

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<sup>54</sup>K. C. Hyams & F. S. Wignall, "War Syndromes and Their Evaluation: From the U.S. Civil War to the Persian Gulf War," Annals of Internal Medicine, vol. 125 (1996), pp. 398-405 and G. P. Chrousos & P. W. Gold, "The Concepts of Stress and Stress System Disorders," Journal of the American Medical Association, vol. 267 (1992), pp. 1244-1252.



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The physiological manifestation of stress in many populations, including veterans, is well-documented. As cited in the Committee's *Final Report*, stress is known to affect the brain, immune system, cardiovascular system, and various hormonal responses. Stress manifests in diverse ways, depending on the individual; without question stress has been scientifically documented to cause headache, diarrhea, sleep difficulties, appetite problems and a broad range of other medical conditions. A stress-induced heart attack or stress-induced diabetes are no less serious or a disease condition because stress *contributed* to the onset. GAO seems to conclude that because some of this research has not been in Gulf War veterans *per se*, but in other human populations, it is not applicable to the current situation; such a position is illogical.

GAO RESPONSE

Stress can be associated with a wide range of physical illnesses, and we do not suggest that illnesses that are stress-induced are any less real. However, we did not find evidence that the broad range of Gulf War veterans' physical symptoms were induced by stress. (See our response to the next comment.)

Even with respect to Gulf War specific investigations, GAO ignores or seems unaware of results from research performed by the Boston VA on a cohort of veterans from Fort Devens, investigations at the New Orleans VA, and studies of individuals involved, for example, with the SCUD missile attack or graves registration. Specifically with respect to PTSD, GAO asserts there are problems in the methods used to diagnose PTSD among Gulf War veterans that might lead to an overestimate of its incidence. Raising the issue of methods to diagnose PTSD is a red herring. The method of diagnosis only would be an issue if different methods were used to diagnose PTSD in Gulf War veterans from those used to diagnose PTSD in controls. In fact, within each of the studies just cited, controls and Gulf War veterans *were part of the same protocol for that particular study*. That is, controls and subjects were treated the same. If GAO opts to dismiss results on PTSD in Gulf War veterans from these varied studies, the criterion put forth in the draft is insufficient to do so.

GAO RESPONSE

We reviewed the reports from the Fort Devens and the New Orleans studies on PTSD, but these two studies provide little support for Committee's conclusion that "stress is likely to be an important contributing factor to the broad range of illnesses currently being reported by Gulf War veterans." First, the primary focus of each of these studies is

the measurement of PTSD. Second, the symptom measures employed in both studies focused selectively on psychological, psychosomatic, and/or stress-related conditions. For example, the New Orleans study employed a checklist inquiring about 20 conditions—11 taken from a scale of psychosomatic complaints and 9 other symptoms that are commonly observed to be stress-related.<sup>55</sup> The samples of deployed troops who indicated high war-zone stress checked more items on this symptom list than those classed as having low or no war zone stress, but 4 to 10 months after the war, only three complaints (nervousness, concentration difficulties, and needing medications to sleep or calm down) showed statistically significant differences based on war-zone stress. Third, no physical examination was conducted in these studies, so it is impossible to determine whether the measured symptoms were selectively related to war zone stress. Fourth, in both studies, there is some possibility that the relationships between war zone stress and symptoms are byproducts of similarities in the methods used to measure them; the Fort Devens study acknowledges some research showing that self-reports of stress are vulnerable to bias from a host of event-related and personal characteristics. Finally, in the Fort Devens study, the total amount of variation in reported symptoms that was explained by the combination of combat exposure stress and a variety of other factors was quite modest (13 percent).<sup>56</sup>

The Committee's remark concerning diagnostic methods suggests that the inclusion of control groups overcomes bias from faulty methods for measuring PTSD. First, the method recognized by experts in the field of PTSD research for conclusively making the diagnosis of PTSD is a psychiatrist's or psychologist's clinical interview following a structured interview protocol, such as the CAPS or SCID. (See app. V, DOD's response to GAO's report.) Of the 18 peer-reviewed studies of Gulf War veterans cited by the PAC report in support of its conclusions on stress, only one used this method.<sup>57</sup> All others relied on psychometric scales. Second, if the deployed veterans suffered subtle neurological damage, for example from chronic pesticide exposures, their scores on the psychometric PTSD scales could be falsely elevated, while those of the nondeployed controls, not exposed to pesticides, would not be. The use of a control group would not correct for this type of bias.

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<sup>55</sup>P. B. Sutker, et al., "War-Zone Trauma and Stress-Related Symptoms in Operation Desert Shield/Storm (ODS) Returnees," *Journal of Social Issues*, vol. 49 (1993), pp. 33-49.

<sup>56</sup>J. Wolfe, et al., "Reassessing War Stress: Exposure and the Persian Gulf War," *Journal of Social Issues*, vol. 49 (4) (1993), pp. 15-31.

<sup>57</sup>S. Perconte, A. Wilson et al., "Unit-Based Intervention for Gulf War Soldiers Surviving a SCUD Missile Attack: Program Description and Preliminary Findings," vol. 6 (1993), pp. 225-238.

In buttressing its argument that the Committee's analysis with respect to stress is flawed, GAO also states it "believes that the use of broad and heterogeneous diagnostic categories in reporting data from DOD's clinical program may contribute to overestimation of the extent of serious psychological illness among Gulf War veterans." It is unclear what GAO means by "broad and heterogeneous diagnostic categories," given the specific nature of the DOD and VA clinical programs. Perhaps GAO believes that DOD and VA physicians participating in these programs have inappropriately or inaccurately diagnosed individuals. If this is the underlying finding to the above assertion, then GAO should document such a finding. Our review of the clinical programs revealed such was not the case, and hence we believe the composition and frequency of diagnoses among clinical program participants is accurately reflected in our Final Report. We re-emphasize that data from the clinical programs cannot be used to represent prevalence of any symptom among the general Gulf War population; only broad-based epidemiologic research can assess this.

GAO RESPONSE

We refer to the use of major diagnostic categories from the International Classifications of Diseases - 9th Revision to report on various types of conditions as a group. For example, the category "psychological conditions" is used to report data from DOD's clinical program. The diagnoses included in the ICD-9 series for psychological conditions cover everything from relatively common, transient, and easily treated conditions, such as tension headache, to more intractable disorders, like clinical depression. It is not clear what clinical or scientific purpose is served by discussing these varied diagnoses as a group.

In the PAC report, under the heading "Data on Stress-Related Disorders" (see p. 71), the Committee notes that "psychological conditions are either the primary or secondary diagnosis in 36.0 percent of CCEP participants," and that "the most common conditions are: major depressive disorder, neurotic depression (also called dysthymia), depression (not otherwise specified), PTSD, anxiety disorders, adjustment disorders, alcohol-related disorders, and substance-related disorders." However, as noted in the footnote to the table on page 72 of the PAC report, the single most common condition in this category is actually tension headache (11.3 percent of CCEP participants and 2.3 percent of registry participants). Apart from tension headache, none of the individual diagnoses listed in this category is the primary diagnosis for more than 3 percent of CCEP registrants.

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GAO states on page 48 that the Committee reported that stress was the risk factor funded for the "greatest portion" of studies, and uses the figure of 32 studies. This characterization is not entirely accurate, given that GAO also concludes that disease hypotheses such as multiple chemical sensitivity have been ignored; in fact, 5 studies on MCS are underway. I believe it would be more accurate to note that 25 of the 107 studies reviewed by the Committee centered on PTSD or stress.

GAO RESPONSE

We quoted from page 34 of PAC's Final Report, "Currently, stress is the risk factor funded for the greatest fraction of total studies—32 studies (30 percent)." However, we have now substituted the figure provided by PAC.

GAO also summarizes the Committee's conclusions about stress in table IV.1, page 70 and offers its own assessment. What is most perplexing about GAO's analysis with respect to stress is its conclusions in this table. GAO's findings here are internally inconsistent with its treatment of stress in the text. In the table, GAO concurs with the Committee's conclusions and notes, "the evidence we reviewed indicates that stress can have an important role in symptoms of many physical illnesses." In fact, GAO goes on to note, "However, when stress is present in a patient with untreated and undiagnosed diffuse physical symptoms, care must be taken to determine whether the stress is the cause or the effect of the physical symptoms." Yet GAO does not acknowledge the Committee offered its perspective on this very matter. Not only do we concur, in fact we reinforced the importance of the thorough medical examination and clinical protocols offered by DOD and VA to address precisely this point—the exams are necessary to rule out underlying disease. We agreed with the Institute of Medicine's finding that the clinical evaluation programs are excellent for the diagnosis of Gulf War veterans' illnesses. Finally, GAO notes in the table that the Committee calls for increased research, yet it fails to acknowledge (in this table or in the text) similar recommendations made by the Committee for low-level health effects of CW agents and synergistic health effects of pyridostigmine bromide and other risk factors.

GAO RESPONSE

As PAC notes, we did not conclude that stress was incompatible or incapable of producing physical symptoms; we concur with PAC's assessment of this matter. However, we do not find that PAC has cited evidence that stress is likely to be an important contributing factor to the

broad range of illnesses that veterans report. We have revised the statement in table IV.1 to clarify this point.

Regarding the health effects of low-level exposure to chemical warfare agents, the Committee suggested in 1996 that "the government should plan for further research on possible long-term health effects of low-level exposure to organophosphorus nerve agents, such as sarin, soman, or various pesticides, based on studies of groups with well-characterized exposures, including (a) cases of U.S. workers exposed to organophosphorus pesticides and (b) civilians exposed to the chemical warfare agent sarin during the 1994 and 1995 terrorist attacks in Japan. Additional work should include follow-up and evaluation of an appropriate subset of any U.S. service personnel who are presumed to be exposed during the Gulf War. The government should begin by consulting with appropriate experts, both governmental and nongovernmental, on organophosphorus nerve agent effects. Studies of human populations with well-characterized exposures will be much more revealing than studies based on animal models, which should be given lower priority." (PAC, Final Report, p. 54)

Accidental and occupational exposures like those cited by PAC are rarely "well characterized," and due to the potentially toxic nature of the exposures, animal studies will be more important to characterizing the effects, particularly synergistic ones. Although PAC concluded that "ongoing federally funded studies should help the scientific community draw conclusions about the synergistic effects of PB and other risk factors" (Final Report, p. 117), we could find no PAC recommendation for additional research on the synergistic health effects of pyridostigmine bromide and other risk factors.

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On page 72, GAO takes detailed issue with the Committee's analysis of studies that have found higher rates of PTSD in Gulf War veterans. GAO claims that the studies we reviewed "have not excluded other conditions that produce symptoms similar to PTSD and can also elevate scores on key measures of PTSD." This is incorrect. The studies reviewed by the Committee used state-of-the-art instruments that have been validated in many other studies. The studies also used the *same* measures for both veterans and controls. Moreover, the studies looked at *several* outcomes: PTSD, depression, alcohol use and abuse, headaches, etc. The investigators did not "bin" symptoms and call everything PTSD so as to elevate these scores, as GAO implies.

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GAO RESPONSE

All but one of the 18 studies on PTSD in Gulf War veterans cited by the PAC report based diagnoses of PTSD on psychometric PTSD scales without confirmatory psychiatric interviews. These instruments are validated for screening, not diagnosis. In addition, care must be taken in evaluating elevated scores that do not surpass validated cut-points for discrimination of PTSD and non-PTSD populations.<sup>58</sup>

GAO further states "Although the reported prevalence rates of PTSD varied from 4 to 32 percent, these rates were based on widely different populations, with high rates of nonparticipation, and little information on selection bias." First, the Committee's review of studies was based on those with high participation rates. Second, GAO fails to note that the important comparison is not PTSD rates between different studies, which are composed of different cohorts. The important comparison is the rate of PTSD among Gulf War veterans compared to the matched control group *within* a particular study group. Moreover, the strength of any research is that findings can be replicated. And in fact, to date the body of epidemiological data on PTSD and Gulf War veterans are quite consistent.

GAO RESPONSE

The PAC states that its review of studies [on PTSD] was based on those with high participation rates. However, most of the cited studies presented PTSD survey data based on samples that were not statistically generalizable. Among those that did employ generalizable samples, participation rates varied from 25 percent to 58 percent, but no comparison of participants and nonparticipants was presented to assess the likelihood of selection bias.

We respond to the Committee's second and third points elsewhere in this appendix.

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<sup>58</sup>See, for example, the discussion by T. M. Keane et al., "Mississippi Scale for Combat-Related Posttraumatic Stress Disorder: Three Studies in Reliability and Validity," Journal of Consulting and Clinical Psychology, vol. 56(1) (1988), pp. 85-90.

GAO also raises as an issue that, "as with most scales and tests, a certain number of people will test positive on any given measure of PTSD even though they do not have PTSD." The Committee does not disagree with this assertion. But GAO fails to then acknowledge that this is why a *control group*, which all studies we reviewed employed, is used to account for "background." Similarly, GAO raises the issue of "false positives," as elevating scores indicative of PTSD. Again, GAO ignores the purpose of *control groups* and that the studies we reviewed had matched control populations.

GAO RESPONSE

Control groups are not a substitute for accurate diagnostic methods. For example, without accurate diagnosis, it is possible that neurological symptoms related to war-related exposures apart from stress will be misattributed to PTSD. In addition, some studies have employed modified PTSD scales incorporating questions that may become markers for recent war participation, rather than evidence of PTSD. These questions would selectively increase scores in the Gulf War group.

- Infectious diseases: GAO asserts on page 6 (and similarly on page 12) that "the Committee concluded that the likelihood of *Leishmania tropica* (a parasitic infection) as an important risk factor for widely reported illness has diminished. However, the extent of asymptomatic leishmania is unknown and the possibility of prolonged latency and apparent clinical dormancy (up to 20 years) of this infection underscores the need to retain Leishmaniasis among the potential risk factors." Again, GAO's statements are unreferenced and inaccurate; they do not reflect accurately the potential risk of leishmaniasis.

GAO RESPONSE

We quote from testimony provided to PAC on March 26, 1996, by Dr. Peter Spencer, who is the principal investigator of a large, federally funded study. As known since 1995 and acknowledged in the PAC report (p. 118), the incubation period for classical visceral leishmaniasis (usually caused by *L. donovani*) may exceed 2.5 years.<sup>59</sup> In addition, the natural history of a newly recognized form of the illness (viscerotropic leishmaniasis) is

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<sup>59</sup>W. H. Jopling, "Long Incubation Period in Kala-azar," *British Medical Journal*, vol. 2:1013 (1955).

unknown.<sup>60</sup> Those whose immune systems become weakened for any reason will be at particular risk. In such patients, the development of visceral leishmaniasis (involving malaise, lassitude, weight loss, splenomegaly, and anemia) up to 20 years after exposure has been documented.<sup>61</sup>

Among the 697,000 Gulf War service members, only 32 cases have been diagnosed: 20 cases of cutaneous leishmaniasis (CL) and 12 cases of viscerotropic leishmaniasis (VL). CL causes a characteristic ulcerative or nodular skin rash that is unlikely to go undiagnosed. VL also demonstrates characteristic symptoms, and while it can be difficult to confirm, 11 of 12 veterans with VL experienced the characteristic signs of VL. Moreover, this Committee, among others, note the physical examinations of the government's clinical programs are of a comprehensive nature that is likely to detect disease due to *Leishmania tropica* infection.

#### GAO RESPONSE

Insofar as no screening or simple diagnostic test is currently available for newly recognized forms of leishmaniasis, there is an insufficient basis to assess the success of the clinical examinations in detecting it. However, this presumption is the primary basis on which the Committee dismisses the notion that leishmania infection is much of a continuing problem. In a March 13, 1997, briefing, experts from Walter Reed Army Institute of Research told us that "most clinicians will fail to recognize 'classic' forms of leishmaniasis, much less atypical clinical presentations." As we note in the report, a CDC analysis appears to concur that the signs of a newly recognized form of the disease are nonspecific and that the diagnosed cases were identified by aggressive case-finding.<sup>62</sup> It stands to reason that diagnosis would be difficult insofar as leishmaniasis is generally unknown in the United States. While PAC concludes that viscerotropic leishmaniasis is not considered to be a cause of widespread illness among Gulf War veterans, PAC acknowledges on p. 118 of its Final Report that "viscerotropic leishmaniasis can be difficult to confirm."

<sup>60</sup>A. J. Magill et al., "Viscerotropic Leishmaniasis in Persons Returning from Operation Desert Storm — 1990-1991," Journal of the American Medical Association, vol. 267 (11) pp. 1444-46.

<sup>61</sup>Badaro, Falcoff et al., "Treatment of Visceral Leishmaniasis With Pentavalent Antimony and Interferon Gamma," New England Journal of Medicine, vol. 332 (1990), pp. 16-21.

<sup>62</sup>"Viscerotropic Leishmaniasis in Persons Returning from Operation Desert Storm—1990-1991" [CDC Editorial Note], Journal of the American Medical Association, vol. 267 (11) (1992), pp. 1444-6.



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Finally, GAO's conclusion that individuals might have dormant infections misses the point. First, GAO fails to acknowledge in the main text that activation and expression of leishmania is of concern in immunosuppressed persons, as noted and referenced in the Final Report, not of general concern. Additionally, the Committee concludes that leishmaniasis is unlikely to be responsible for the types of symptoms currently being reported in Gulf War veterans today. GAO documents no scientific evidence that leishmaniasis results in the range of symptoms currently associated with undiagnosed illnesses. GAO can insist that leishmaniasis is, hypothetically, of significant future concern, but it needs to do so despite the current statistics. Further, GAO should acknowledge either that current symptoms and illnesses among veterans are separate from future leishmaniasis, or it should provide data that document why GAO believes it is a real-time problem. (When GAO addresses the matter of latent infections in the appendix, it states [without reference] leishmania is reemerging in AIDS patients in Europe—hardly a comparable population to compare to Gulf War veterans.)

GAO RESPONSE

We have modified the statements in our letter summarizing our findings to match the statement in appendix IV, which incorporates the role of the weakened immune system. It is in cases in which the patient's immune system becomes deficient that such reexpression of previously asymptomatic infection is a concern.<sup>63</sup> However, because it is not possible to predict which persons' immune systems may become weakened, we believe that it is important for all veterans and health care professionals to understand the significance of such potential infection. In addition, the natural history of the viscerotropic form of leishmaniasis is not well understood; that is, little is known about the length of incubation and the course of disease.<sup>64</sup>

While it could be consistent with some of the Gulf War veterans' symptoms, we do not contend in our report that leishmaniasis—or any other illness of which we are aware—would explain the range of symptoms currently being reported in the veterans.

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<sup>63</sup>See, for example, A. J., Magill, et al., "Visceral Infection Due to *Leishmania tropica* in a Veteran of Operation Desert Storm Who Presented 2 Years After Leaving Saudi Arabia," *Clinical Infectious Diseases*, vol. 19 (Oct. 19, 1994), pp. 805-6. These authors note, "...the presence of a cofactor depressing cell-mediated immunity (malnutrition, immunosuppressive drug treatments, AIDS, or malignancy) can lead to symptomatic leishmanial disease..." See also, R. Badaro, et al. "Leishmania donovani: An Opportunistic Microbe Associated With Progressive Disease in Three Immunocompromised Patients," *Lancet*, vol. 1 (1986), pp. 647-9.

<sup>64</sup>Even infection with the same species of parasite (*Leishmania donovani*) can take widely different courses (see Badaro et al., "New Perspectives on a Subclinical Form of Visceral Leishmaniasis," *The Journal of Infectious Diseases*, vol. 154(6), pp. 1003-1011.).

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We noted the reemergence of leishmaniasis in Europe in the context of noting that the infection can flare when the immune system is weakened; the comparability of the exposed groups is not relevant to the point that we were making.<sup>65</sup>

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Again, GAO's reference in table IV.1 (page 70) to the possibility of future concern about leishmaniasis obscures the point that the Committee's conclusion pertains to illnesses being reported today. In noting evidence of Q fever and sandfly fever, GAO should be cautious in linking such cases to Gulf War service, since some Gulf War veterans have since been deployed to other theaters where these diseases also are endemic.

GAO RESPONSE

We presume that veterans are concerned about their future health as well as their current health. In the absence of simple diagnostic tests, it is difficult to judge the extent of current illness attributable to leishmania infection.

The more important point is whether these veterans are ill as a result of their exposure. The risk of sandfly fever to U.S. troops in the Gulf was believed to be high. Although we recognize that it is possible that some of these veterans may have been deployed to other areas in which they might have contracted this disease, the blood samples that CDC analyzed were taken after their return to the United States from the Gulf.

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<sup>65</sup>See, for example, Phillip G. Lawyer, "Leishmaniasis Update," Proceedings of the 1995 DOD Pest Management Workshop (1995), p. 3 (<http://www.afpmb.acq.osd.mil/pubs/present/htm>). He states, "The emergence of VL [viscerotropic leishmaniasis] as a serious opportunistic infection in AIDS patients in Europe has alarming implication for leishmaniasis endemic areas where the prevalence of HIV infection is increasing (Africa, Brazil, Indian subcontinent)."

On page 74, to bolster the argument that stress has been overemphasized and alternatives not fully explored, GAO returns to the issue of infectious disease. Specifically, the draft quotes from a Walter Reed document that notes acute sandfly fever can lead to complications of depression, fatigue, and weakness. The Committee does not disagree, but the point is there have been no acute cases of sandfly fever reported for Gulf War veterans. GAO goes on to state that "a CDC analysis of blood taken from 158 Pennsylvania Air National Guard members found that 5.7 percent showed evidence of previous sandfly fever infection." GAO acknowledges the difficulty in interpreting this finding. More importantly, we further note that the principal investigator of this study reported to the Committee that the rates of positive detection were the same between sick and healthy individuals in this Pennsylvania Air National Guard population.

GAO RESPONSE

Medical surveillance during the war was imperfect. While some reports indicate no cases of sandfly fever, at least six cases of febrile illness compatible with sandfly fever were reported among soldiers of the 1/505 PIR on September 22, 1990, by a preventive medicine officer. In addition, the risk of sandfly fever was believed to be high. A December 1991 Defense Intelligence Agency report presented tests of blood samples from Iraqi military personnel involved in the Gulf War. These tests were conducted to help identify biological warfare agents in the Iraqi inventory and assess the prevalence of endemic diseases. In discussing naturally occurring diseases, the report notes, "The large percentage of positive reactions to sandfly fever (Sicilian and Naples strain) confirms the high risk this disease poses for US military operations in the region." For the Sicilian strain, 98 of 125 samples were positive, and 49 of 126 samples were positive for the Naples strain. (In contrast, only 21 of 130 samples were positive for exposure to Q-fever.) Thus, if there were no cases of sandfly fever, it seems difficult to explain their complete absence.

It is true that the presence of evidence of exposure to sandfly fever did not distinguish persons with the cluster of fatigue symptoms defined by CDC from persons who did not fit this definition. However, this does not obviate the need to exclude such infection in diagnosing particular veterans' fatigue and posttraumatic symptoms. Sandfly fever would not consistently result in such complications, though it might sometimes be responsible for them.

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For the record, we note that GAO reports on infectious disease tests in military working dogs. The Committee was aware of these studies, but as these results went unpublished, and hence have not been subjected to peer review, the Committee did not report on them.

- Exposure to chemical warfare agents: Also on page 6, GAO states, "the Committee concluded, even in the absence of credible exposure data, that it was unlikely that the health effects reported by Gulf War veterans are the results of exposure to organophosphates or mustard or chemical warfare agents. There is substantial evidence that such compounds are associated with delayed or long-term health effects similar to those experienced by the Gulf War veterans."

First, GAO again fails to present references that document its "substantial evidence." Second, GAO mischaracterizes the Committee's conclusion (elaborated further below). Third, the draft implies that all of these agents are associated with long-term health effects of a similar nature, which is false. Fourth, the text as drafted fails to distinguish between the agents and their possible health effects, today, versus possible future health effects—in particular with mustard agent, about which the Committee makes recommendations that GAO does not note. Fifth, GAO completely ignores the fact that the Committee carefully reviewed (and cited) a vast body of scientific literature to reach its conclusions based on *current* evidence, but that the Committee also recommended increased funding to study health effects of low-level exposure to chemical warfare (CW) nerve agents. GAO fails to note that the Committee made recommendations for specific research on those veterans presumed to have been exposed (e.g., at Khamisiyah) and/or other individuals involved in documented sarin exposures (e.g., the Tokyo subway attack). GAO also ignored the Committee's conclusion that "DOD's intransigence in refusing to fund such research [on possible long-term health consequences of low-level exposure to CW agents] until summer 1996 has done veterans and the public a disservice."

GAO RESPONSE

First, references have been provided in footnotes 28-36 of appendix III.

Second, our specific responses to the claim that we have mischaracterized the Committee's conclusions are set forth below.

Third, we have clarified statements that may have led the Committee to infer that we claimed that all organophosphates compounds produce similar long-term effects.

Fourth, we are careful to distinguish between those individuals who are ill today and individuals who may become ill in the future. For example, our discussion of aflatoxin is largely about potential cancers in the future.

Fifth, as directed by Congress, we conducted our own independent, objective review. Our review included reviewing reports and scientific literature, interviewing researchers, and analyzing the information

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available to us. Through this review we reached different conclusions from those of the PAC. In any event, given PAC's finding that minimal research is available on the health effects of low-level exposure, it is difficult to understand the rationale for its conclusion that chemical warfare agent exposures are unlikely to be consistent with veterans' health complaints. Moreover, we note that findings of some studies on such low-level exposures are not supportive of such a conclusion.

We respond to PAC's remarks concerning its recommendations elsewhere in this appendix.

Insofar as the Committee clearly feels strongly about the need for additional research, we find it difficult to understand the rationale behind PAC's conclusion that it is unlikely these exposures could have contributed to veterans' health complaints.

The reference "even in the absence of credible exposure data" is specious and misleading, meant to cast doubt on the Committee's work while ignoring the analytic framework we adopted. In fact, the Committee erred in veterans' favor and did not assess possible health effects based on documentation, or lack thereof, of in-theater exposure to any risk factor we evaluated. As the report notes, "our analysis of possible health effects was performed independently of whether exposures were undocumented, imprecise, or known." For every risk factor we report on, including organophosphate (OP) nerve agents and mustard agents, the Committee considered the possible health consequences of a range of scenarios from high-level to low-level exposure and single to multiple events of chronic/continuing exposure. Put another way, this Committee assumed exposure occurred and then asked the question: What short-term and long-term health effects would one expect to observe?

GAO RESPONSE

PAC's (first) comment incorrectly misinterprets our point. As noted, PAC formed some of its conclusions in the absence of exposure data. However, we have removed the quotation.

Some of the Committee's conclusions are inconsistent with the results of applying its analytic framework. For example, it is difficult to understand why the Committee concludes that the agent in question is "unlikely" to have contributed to the health problems reported by veterans even as it recognizes the need for data on the health effects of low-level exposure.

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GAO's reference to "unanswered questions" on page 6 is curious. Since GAO identifies "the extent to which veterans may have been exposed to chemical agents as a result of fallout from the destruction of suspected chemical weapons storage sites" as an open issue, one might conclude GAO expects this question is answerable and that research can be directed based on an answer. This Committee concludes otherwise, and we do not believe research should wait while an answer is sought. To the contrary, the Committee called attention to the adverse consequences on DOD's research prioritization of such logic (i.e., waiting for answers about CW exposures). Again, the Committee noted that DOD's delay in funding research on low-level health effects—even in the absence of exposure data—was unjustified. I elaborate on this issue below in greater detail.

GAO RESPONSE

As we noted in an earlier report, "available bomb damage assessments during the war concluded that 16 of 21 sites categorized by Gulf War planners as nuclear, biological, and chemical (NBC) facilities had been successfully destroyed. However, information compiled by the United Nations Special Commission (UNSCOM) since the end of Desert Storm reveals that the number of suspected NBC targets identified by U.S. planners, both prior to and during the campaign, did not fully encompass all the possible NBC targets in Iraq." UNSCOM has conducted investigations at a large number of facilities suspected by the U.S. authorities as being NBC related. Regarding the few suspected weapons sites that have not yet been inspected by UNSCOM, we have been able to determine that each was attacked by coalition aircraft during Desert Storm and that one site is located within the Kuwait theater of operations in closer proximity to the border, where coalition ground forces were located. However, we have yet to learn why these facilities have not been investigated.<sup>66</sup>

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<sup>66</sup>See Operation Desert Storm: Evaluation of the Air Campaign (GAO/NSIAD-97-134, June 12, 1997, p. 2).

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On page 13 GAO again notes, "Evidence from various sources indicates that chemical agents were present at Khamisiyah, Iraq and elsewhere on the battlefield. The magnitude of the exposure to chemical agents has not been fully resolved." As just stated, the magnitude of the exposure need not be resolved before funding on low-level health effects of CW agents is initiated, as recommended by the Committee. Since GAO repeatedly questions the Committee's work in this regard, one must conclude that GAO suggests the government should not fund such research until the magnitude of exposure issue is resolved—and on page 83, GAO all but says such research is a wasted effort. The Committee disagrees strongly with such a proposal. Dr. Philip Landrigan, an international expert in both toxicology of low-level health exposures and epidemiological research and Committee member, recently noted at the Committee's meeting in March 1997 how such research could be performed and could be quite illuminating. Similarly, GAO's reasoning in table IV.1 to dispute the Committee's assessment of health effects of CW agents is outrageous. This Committee was a driving force for DOD's admission regarding Khamisiyah and the presence of nerve agents. GAO implies that the Committee ignored this information, when we were responsible in large measure for the revelation. Again, GAO completely disregards the fact that, as reported in the Final Report, the Committee erred in veterans' favor and did not assess possible health effects based on documentation, or lack thereof, of in-theater exposure to CW agents. Instead, we assumed exposure and assessed what short- and long-term health effects would be expected.

GAO RESPONSE

PAC has misinterpreted our position on the proper sequencing of studies. Research into the nature of the health effects of agents to which troops may have been exposed during Operation Desert Storm should not wait for accurate answers to questions of the magnitude of actual exposures. We neither state nor imply otherwise.

In its reference to a statement we made in table IV.1, we made that statement to provide background for our assessment. We have deleted the word "given," which may have left the incorrect impression that the Committee did not take account of the presence of chemical warfare agents at Khamisiyah and elsewhere on the battlefield.

Numerous studies in humans and animals report that survival from severe, immediate poisoning by OP nerve agents (including OP pesticides) can be associated with measurable, long-term neurological effects. The Committee concluded that the available scientific evidence does not indicate that such long-term effects occur in humans following low-level exposures, but data from human or animal research are minimal. Hence, we recommend additional research in this area.

GAO RESPONSE

We cite animal studies showing that exposures to certain organophosphate agents at levels that do not cause acute poisoning are associated with measurable long-term effects. It appears inconsistent for the Committee both to conclude that exposures to organophosphate agents are unlikely to have contributed to veterans' health problems and simultaneously to recognize the existence of minimal research on low-level exposure—the most likely exposure scenario for organophosphate pesticides.

The Committee may have overlooked a set of articles published in peer-reviewed journals by Husain et al. addressing the chronic neurotoxicity of low-level exposure to sarin. In these studies, the investigators exposed hens and mice, in separate experiments, daily for 10 days to sub-acute doses of sarin orally and through inhalation. The animals did not require protection by simultaneous administration of atropine and pralidoxime, often used in high-dose experiments. Fourteen days after the start of the daily exposures, some of the animals developed effects (for example, ataxia, muscular weakness), suggesting that sarin can induce OPIDN. These studies have been discussed since they were published in 1993, 1994, and 1995, and they have received no serious criticism of which we are aware. It appears that DOD, PGVCB, and PAC have not recognized and commented on them, while continuing to insist that there is no evidence that low-level sarin can cause chronic neurotoxicity in the absence of severe immediate effects.

On page 51, GAO reports on a study purporting to demonstrate long-term EEG changes in primates after low-level doses of a CW agent (sarin). GAO, however, does not note that the authors stated in the published report that the "results were inconclusive." Moreover, the Committee reviewed a more recent report—from the same scientists—that studied 77 industrial workers exposed to levels of sarin that caused immediate toxicity. One year later slight alterations in the EEGs were noted. The study also documented, however, that trained experts could not distinguish an individual EEG from an exposed worker from an EEG of a person who had not been exposed. The researchers also found, but GAO failed to report, that they found no clear relationship existed between alterations in EEG spectrum and alterations in brain function.



GAO RESPONSE

The comment by PAC reflects a selective reading of the work by Duffy and Burchfiel in the area of the EEG effects of organophosphates. Indeed, the authors characterized one of the tests that they conducted on the EEGs of treatment and control groups as "inconclusive."<sup>67</sup> However, they also reported statistically significant differences between the two groups on several other measures, such as the increase in the amount of beta activity in EEGs and an increase in rapid eye movement sleep. The authors concluded that, "Our EEG findings and the psychological reports in the literature provide parallel warnings of possible long-term CNS toxicity of OP agents."<sup>68</sup> Additionally, in recent testimony before the House Committee on Government Reform and Oversight, Professor Duffy made the following observations, which support our conclusions about the effects on the behavior of organophosphates (including sarin):

"It is quite possible to have a biologically significant exposure to OP compounds and not be aware of it...Sarin can produce long term alteration of brain function. Levels of exposure capable of producing such late effects may not be recognizable by subjects, especially if they are unaware of what is happening and/or are distracted by other activities."<sup>69</sup>

The Armed Forces Epidemiological Board also reviewed these studies and found that, "they represent reasonable evidence that even small doses (exact level is unknown) may result in EEG changes."<sup>70</sup>

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<sup>67</sup>James L. Burchfiel, et al., "Organophosphate Neurotoxicity: Chronic Effects of Sarin on the Electroencephalogram of Monkey and Man," Neurobehavioral Toxicology and Teratology, vol. 4 (1982), pp. 767-778.

<sup>68</sup>Ibid., p. 777.

<sup>69</sup>Frank H. Duffy, M.D. (Department of Neurology, Harvard Medical School), "Evidence that Minor Exposures to the Nerve Agent Sarin May Lead to Long Term Difference in Brain Function," testimony provided to the House Committee on Government Reform and Oversight, Jan. 19, 1997.

<sup>70</sup>Environment Committee, Armed Forces Epidemiological Board, Long-term Health Effects Associated with Sub-clinical Exposures to GB and Mustard, p. 6.

On page 52, the draft cites a project that was published after our Final Report, but Dr. Landrigan did write an editorial about this work with which we concur. He noted the studies "have limitations that substantially weaken the authors' strong conclusions." In this regard, Dr. Landrigan noted the studies are on a single battalion, and hence not generalizable to the broader population of Gulf War veterans. Additionally, the low participation rate (41 percent) raises the issue of selection bias—i.e. those who participated might be significantly different in certain important characteristics even when compared to other individuals who belonged to the battalion but who chose not to join the study. In fact, only 43 percent of nonparticipants who were surveyed reported serious health problems, whereas 70 percent of participants did so. Also, information on illnesses was self-reported. Detailed clinical examinations were performed for just 23 symptomatic veterans, less than 4 percent of the battalion, and classic tests to confirm certain neurological damage were made on only 5 veterans. Another significant limitation is that all exposure data were self-reported, and no effort was made to independently or objectively verify exposures. In addition to Dr. Landrigan's review, Committee staff and other experts have noted that among the individuals who participated in neurological testing, neurologists and study investigators were unable to distinguish ill veterans from "well" veterans based on clinical laboratory findings. In other words, the findings were nonspecific and of unknown clinical relevance. *More to the point, GAO's analysis concerning the Haley studies is internally inconsistent in this draft. The very things—lack of exposure data, poor response rate, etc.—about which GAO criticizes the current epidemiologic research (concluding it all but pointless), are wholly applicable to the Haley work, yet GAO overlooks these factors as they apply to this matter.*

My comments on long-term health effects in the context of GAO's specific reference to organophosphorous (OP)-induced delayed neurotoxicity follow in a later section.

#### GAO RESPONSE

We have cited the work of Dr. Haley and his colleagues as a positive example of an attempt to refine a case definition in the presence of diffuse and nonspecific symptoms. His approach, to look for patterns of correlation among the reported symptoms and explore their relationship with exposure history, is a reasonable and rational first step upon which others might build. We discussed Dr. Haley's approach with two leading epidemiologists, who agreed that the approach Dr. Haley had taken was reasonable in an instance in which a case definition was difficult to derive. In fact, elsewhere in the aforementioned editorial, Dr. Landrigan concurs with the major thrust of our position:

"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... Further research is

needed to determine whether low-dose exposure to chemical warfare agents can cause chronic neurotoxicity.<sup>71</sup>

We agree with Dr. Landrigan on this point. It is also our contention, based on the evidence presented in our report, that the federal research program has not pursued this question with sufficient energy.

It is apparent to us, based on the literature that we reviewed and the references cited, that the hypothesis that some veterans' illnesses are OPIDN or similar to OPIDN that may stem from exposure from pesticides, chemical warfare agents, or pyridostigmine bromide while on duty in the Persian Gulf is a plausible hypothesis. We disagree with PAC's conclusions that these are unlikely exposure scenarios for the illnesses being experienced by veterans. Moreover, we fail to understand the Committee's rationale for endorsing additional studies in this area after discounting the likelihood of the hypothesis. In fact, it should be noted that CDC took similar steps to construct a case definition in its review of symptoms reported by a large group of Gulf War veterans. Dr. Haley's work has apparently generated plausible hypotheses for further exploration and testing.

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- Aflatoxin and biological warfare agents: On page 6, GAO states a second unanswered question revolves around "veterans' possible exposure to the biological agent aflatoxin, the health effects of which may not be known for months, or even years, after exposure." The draft does not articulate the reason this question is raised, nor does it acknowledge that the Committee's Final Report reviews this issue. As drafted, GAO appears not to attribute aflatoxin to the range of symptoms currently being reported by Gulf War veterans, and the scientific literature cited in the Committee's report would support such an interpretation. It is unclear from GAO's draft, however, whether GAO recommends specific action concerning aflatoxin. For the record, the Committee's Final Report found the best available evidence to date, including U.N. inspections, indicates U.S. personnel were not exposed to biological warfare agents during the Gulf War. Even so, the Committee assessed the documented health effects of aflatoxin, noting scientific data suggest aflatoxin causes liver cancer in humans. Hence, we recommend epidemiologic studies of Gulf War veterans to assess whether there is an increased prevalence of liver cancer years to decades following the War; such studies, however, are the very type that GAO dismisses.

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<sup>71</sup>P. J. Landrigan, Illness in Gulf War Veterans. Journal of the American Medical Association, vol. 277 (1997), pp. 259-261.

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GAO RESPONSE

Concerning exposure to aflatoxin, for the reasons cited earlier, we can neither confirm nor rule out veterans' exposure to this agent. The Central Intelligence Agency has noted that the health effects of exposure to aerosolized aflatoxin are poorly understood.

Descriptive studies of clearly defined endpoints may be useful in providing assurance that large numbers of veterans are not suffering the health problems characteristic of aflatoxin exposure. However, it is important to note that only in the instance of widespread exposure would this approach resolve the issue of whether particular veterans' health problems are attributable to their Gulf War service.

In response to the general comment concerning the value of epidemiologic studies of Gulf War veterans, we agree that some basic descriptive information on veterans' health may be useful, to include the cancer surveillance studies identified by PAC, for the purpose of providing veterans with information about the presence of widespread and serious health effects. However, it will be very difficult for these studies to resolve the issue of whether specific veterans' health problems are related to their Gulf War service in the absence of (a) widespread exposure; (b) biomarkers for exposure; or (c) better data on who was exposed and at what levels.

These comments apply also to text on page 12, where GAO again notes that the effects of "at least one biological agent . . . would not be observed for many years." GAO's statement, in fact, concurs with the Committee's finding that aflatoxin is not causally linked to symptoms currently reported by Gulf War veterans. Yet, GAO makes no mention of the Committee's work, instead implying that we ignored the important issue of biological warfare agents.

Additionally, GAO characterizes the Committee's work on biological warfare agents in table IV.1 (page 70) and on pages 78-81. In its assessment, GAO ignores the fact that this Committee in its Interim Report found that the United States' real-time biological warfare agent capability constituted a serious deficiency. As before, GAO's reference in the table to aflatoxin as a possibly *future* concern obscures the point that the Committee's conclusion on biological warfare agents pertains to illnesses being reported *today*. The table again fails to acknowledge that the Committee noted that aflatoxin was a suspected human carcinogen and, in fact, recommended long-term followup.

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**Appendix VII  
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Committee on Gulf War Veterans' Illnesses**

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GAO RESPONSE

We have added text to note the Committee's findings. The PAC concluded, "Aflatoxin...is a liver carcinogen, and increased rates of liver cancer could result decades following low-level exposure, although available evidence reviewed by the Committee does not indicate such exposures occurred during the Gulf War." (PAC, Final Report, p. 112.) GAO considers exposure to aflatoxin as an unresolved issue.

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- Page 7: "As a result of the misplaced focus and methodological limitation of government research on Gulf War veterans' illnesses, this research is not likely to identify the potential causes of the illnesses." GAO fails to articulate how this could be accomplished, other than via epidemiologic research. If GAO believes the entire research portfolio should be directed to examining toxicologic effects—in the absence of any underlying, scientific basis to evaluate the relative importance of a risk factor—it should state such a position directly.

GAO RESPONSE

We have added text to clarify our position regarding the likely utility of further epidemiologic research in light of the absence of adequate exposure data.

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- Page 8: "The focus of federal research has primarily been the epidemiological study of the prevalence and cause of Gulf War illnesses, rather than the diagnosis, treatment, and prevention of them. . . . While the multiple studies of the role of stress in the veterans' illnesses have been supported with federal research dollars, other hypotheses have been pursued largely outside the federal research program." These statements, at best, are overstatements. As the Committee report clearly documents, of 107 studies, 18 studies are devoted to general epidemiology and Gulf War veterans' health status per se; 25 focus on PTSD and stress per se; and the balance focus on the broad range of commonly suspected Gulf War risk factors and/or studies to assess cancer, multiple chemical sensitivity, chronic fatigue syndrome, or fibromyalgia.

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GAO RESPONSE

We used the methodological categorizations identified by PGVCB as reported for each study in PGVCB research plans and reports to Congress. The categories identified by PAC appear to be an amalgam of methodological approaches and topical emphases.

- Although the issues bulleted on pages 12-13 are raised elsewhere, separately, I flag them here because it is unclear their purpose in the manuscript. Is GAO's "review of the conclusions made by the Presidential Advisory Committee" intended to rebut the Committee's findings on these issues? The presentation is not at all coherent if that, indeed, is the goal.

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GAO RESPONSE

Appendix IV contains a more detailed discussion of the PAC's conclusions and our assessments.

- On page 13, GAO raises the issue of delayed neurological effects, "Exposure to pesticides can induce a delayed neurological condition without causing immediate symptoms." This sentence is misleading. There is no scientific basis for the implication in the GAO draft that OPIDN might be expected in Gulf War veterans exposed to asymptomatic doses of pesticides used during the Gulf War. Most OP pesticides do not cause the delayed neurological condition known as OPIDN under any exposure scenario situation up to lethality. As we note, a few OP pesticides can cause OPIDN in laboratory animals only if the animal is kept alive with special drugs. The OP pesticides available to U.S. service members during the Gulf War were the same as those commonly used without special licensing in the United States. More importantly, EPA registers these pesticides—a process that requires evidence the pesticide does not cause OPIDN.

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GAO RESPONSE

Our specific rebuttals to PAC's individual assertions on these matters are set forth below.

Similarly, GAO's conclusions about pesticides as a risk factor in table IV.1 are speculation and not supported by the extensive scientific literature on delayed neurotoxicity with certain OP agents. Although certain OP agents cause delayed neuropathy without showing initial acute poisoning symptoms, none of the pesticides available to U.S. service members in the Gulf was in this category. Also, GAO's suggestion in this table that PB might enhance the delayed neurotoxicity of certain OP agents is only a suggestion: it also has been suggested PB might cause the opposite effect—i.e. protect against delayed neurotoxicity. There are no published data showing that PB pretreatment will cause an OP agent that doesn't normally cause delayed neurotoxicity, to suddenly cause that effect. The only data about synergism between PB, permethrin and DEET were done with laboratory animals and involved acutely toxic doses with immediate symptoms, including death.

GAO RESPONSE

Concerning delayed neurotoxic effects of organophosphates, not all organophosphates cause these effects; however the Committee is incorrect in implying that pesticides to which U.S. service people were exposed in the war could not have caused delayed neurotoxicity.<sup>72</sup> As PAC reports on p. 97 of its Final Report, Chlorpyrifos (Dursban) was shipped to the Gulf. Dursban has been linked to delayed, chronic neurotoxicity in laboratory animals. In the past, the delayed, chronic neurotoxic potential of chlorpyrifos was overlooked.<sup>73</sup> The Environmental Protection Agency has recently penalized the manufacturer for failing to promptly report human injuries from this pesticide and suggested that the pesticide be relabeled to withdraw it from many applications, a decision with which the company acquiesced. In addition, other unknown pesticide chemicals may have been brought from the United States or purchased from local suppliers in Saudi Arabia by troops outside the command structure; these cannot be enumerated by DOD.

Regarding pyridostigmine bromide pretreatment, while pretreatment with pyridostigmine bromide does not potentiate chronic neurotoxicity from subsequent organophosphate exposure, studies of similar drugs indicate that treatment after a sufficient organophosphates exposure may potentiate

<sup>72</sup>M. Lotti, "The Pathogenesis of Organophosphate Polyneuropathy," Critical Reviews in Toxicology, vol. 21 (1991) pp. 465-487 (esp. pp. 466-7, 472); J.G. Kaplan et al., "Sensory Neuropathy Associated With Dursban (Chlorpyrifos) Exposure," Neurology, vol. 43 (1993) pp. 2193-96; C.S. Petty, "Organic Phosphate Insecticide Poisoning," American Journal of Medicine (Mar. 1958), pp. 467-70; E. Capodicasa, et al., "Chlorpyrifos-induced Delayed Polyneuropathy," Archives of Toxicology, vol. 65 (1991), pp. 150-155; J. Rosenberg, "Organophosphate Toxicity Associated with Flea-Dip Products — California," Journal of the American Medical Association, vol. 260 (July 1, 1988), pp. 22-3.

<sup>73</sup>M. Lotti, "The Pathogenesis of Organophosphate Polyneuropathy," Critical Reviews in Toxicology, vol. 21 (1991), pp. 465-587 (especially pp. 467 and 473).

chronic neurotoxicity.<sup>74</sup> There is evidence from laboratory studies that post-exposure treatment can cause chronic neurotoxicity to occur with organophosphate doses that would ordinarily be too low to cause a problem (pharmacologic "promotion"), or it could turn a mild case of organophosphate-induced chronic neurotoxicity into a severe case (pharmacologic "potentiation"). Several papers have appeared on this subject since 1990, although studies of post-exposure promotion by pyridostigmine per se have not been undertaken as far as we know.

In response to the committee's assertion that the only evidence for synergism among pyridostigmine bromide, permethrin, and DEET is from in vivo bioassays using lethal doses, Haley et al. found epidemiologic evidence that pyridostigmine toxicity and a chemical nerve agent may have acted synergistically to cause a syndrome they labelled "confusion-ataxia," the most severe of the three primary syndromes they identify.<sup>75</sup> They also found both pyridostigmine toxicity and DEET exposures to be strongly associated with their syndrome 3 (arthro-myo-neuropathy). In any event, standard risk analytic practice involves study of interactive effects in laboratory animals at doses that result in acute toxicity and to further characterize the relationship from that point. We have made the point that further study of the effects of this as well as other exposures is warranted.

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- Also on page 13, the GAO draft notes, "available research indicates that exposure to pyridostigmine bromide can alter the metabolism of organophosphates in ways that enhance delayed, chronic effects on the brain." Studies that report this effect were based on use of laboratory animals, e.g. cockroaches, chickens, and rats, not humans. The doses used in these laboratory experiments were far greater than the amounts to which U.S. service members in the Gulf could have been exposed; the studies used routes of administration, e.g. oral, under the skin, that are not comparable to the possible routes of exposure of Gulf veterans. Furthermore, the completed peer-reviewed studies examined by the Committee were unable to present findings that could address what effect PB, DEET, and permethrin would have on the morbidity of these combinations in humans and what illnesses might be induced by such exposures.

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<sup>74</sup>Op cit., M. Lotti, p. 473; C. N. Pope & S. Padilla, "Potentiation of Organophosphorus-Induced Delayed Neurotoxicity by Phenylmethylsulfonyl Fluoride," Journal of Toxicology and Environmental Health, vol. 31 (1990), pp. 261-73.

<sup>75</sup>R.W. Haley and T.L. Kurt, "Self-reported Exposure to Neurotoxic Chemical Contamination in the Gulf War," Journal of the American Medical Association, vol. 277 (1997) (3), pp. 231-237.



GAO RESPONSE

We are uncertain what type of evidence PAC would consider sufficient to conclude that some effect might have occurred. While studies testing the toxic effects on humans have not been conducted, available animal studies provide reasonable evidence of negative effects that make it premature to conclude this is not a serious a risk factor and indicate that further research should be conducted. For obvious ethical reasons, it is not possible to conduct experimental studies on humans of effects that are feared to be toxic; thus, standard toxicological approaches used by the government and the private sector focus on research with animals. Researchers have shown that the neurotoxic phenomenon produced by organophosphate nerve agents in some poultry varieties was comparable to the manifestations produced in man.<sup>76</sup> In this regard, it is known that organophosphate compounds that are neurotoxic to chickens will also produce neurotoxicity in humans under appropriate conditions.

For example, the laboratory studies published by Abou-Donia et al. demonstrated that pyridostigmine, chlorpyrifos, permethrin, and DEET can synergistically act to cause delayed, chronic neurotoxicity. The hen is the EPA-required laboratory model for testing chemicals for the potential to cause OPIDN. Testing these chemicals for synergism in humans would have been highly unethical. The doses of permethrin, DEET, chlorpyrifos and pyridostigmine were intended to be in the range of sublethal human exposure. Given the severity of the OPIDN that occurred with chemical combinations in the doses used, it is possible that lower, but still medically significant, levels of damage would follow even with slightly lower doses of pyridostigmine.

The Abou-Donia group administered pyridostigmine bromide orally; Gulf War veterans likewise were administered pyridostigmine orally. The permethrin, chlorpyrifos, and DEET were injected by needle into the skin just under the surface (intradermally) to simulate the probable absorption through the skin. Since under their feathers hens have thicker skin than humans, it is common laboratory practice to deliver skin exposure to hens by intradermal injection. We believe the Committee erred in not considering the findings of the Abou-Donia et al. studies to be indicative of expected effects on humans.

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<sup>76</sup>Stockholm International Institute for Peace Research (SIPRI), Delayed Toxic Effects of Chemical Warfare Agents (New York: Alonquist and Wiksell International, 1975).

With respect to PB, GAO adds emphasis in table IV.1 to the Committee's finding and should acknowledge that this emphasis is GAO's, not ours. In reporting how the Committee reached its finding, GAO cites only the use of PB in myasthenia gravis patients and ignores the additional evidence we critiqued and documented on use in non-patients, including data that demonstrate that when drug use is discontinued, *short-term* effects reverse without documented delayed effects. *Long-term* side effects in humans have not been documented. GAO states research in this field is in flux and that it defers judgment on PB, singly. First, GAO fails to document why it believes it is in flux. Second, GAO skirts the question of what is known based on *currently available scientific evidence*. Again, from decades of clinical use and research studies, physicians and scientists have extensive knowledge of PB's mechanism of action and known physiologic effects. Finally, GAO's assessment states "delayed neurotoxic effects" in humans exposed to PB in combination with DEET and permethrin have been clinically observed, but no reference is supplied. In fact, some have *speculated* about this, but human experimentation in this regard has not occurred, nor has a retrospective causal linkage for these agents been established in humans.

GAO RESPONSE

We are unaware of studies specifically testing, with sufficiently sensitive neurophysiologic techniques, for long-term neurotoxic side effects of pyridostigmine in any prior population taking pyridostigmine regularly. We are, however, aware that patients taking pyridostigmine are cautioned to avoid exposure to malathion, which was among the pesticides sent to the Gulf.<sup>77</sup>

Concerning the Committee's assertion that research is in flux, pyridostigmine bromide may have been used in the presence of contraindicated coexposures (malathion) and may potentiate the effects of Dursban.

In response to the Committee's point about delayed neurotoxic effects, we have modified our statement to read, "delayed neurotoxic effects in humans exposed to PB and DEET have been epidemiologically inferred and reproduced in hens." Human epidemiologic evidence of the synergistic effects of pyridostigmine, DEET, chlorpyrifos, and chemical nerve agents has been presented for an epidemiologic association between patterns of complaints and reported exposures of these agents in humans.<sup>78</sup>

<sup>77</sup>"Pyridostigmine," in *Clinical Pharmacology* (Online—<http://www.cponline.gsm.com>), Gold Standard Multimedia Inc., 1994.

<sup>78</sup>Op cit., Haley et al.

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- On page 14, GAO notes that its second objective concerned the review of the Persian Gulf Veterans Coordinating Board's research strategy, and for this reason GAO reviewed the work of this Committee. I note again, that the draft text makes no reference to a GAO analysis of the Committee's findings and recommendations with respect to *research*. The work cited by GAO in this draft pertains to our assessment of *exposures and risk factors*. I strongly encourage GAO to review the Committee's efforts in the Final Report and Interim Report on the relevant topic—research. The only mention made of this work is table III.3 on page 45.

GAO RESPONSE

We respond to PAC's remarks concerning its recommendations elsewhere in this appendix.

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- On page 68, appendix IV, "Support for Key Government Conclusions is Questionable," GAO again reviews the Committee's work on risk factors, only. First, GAO fails to even acknowledge that the Committee made findings and recommendations in the areas of research, outreach, clinical care, and chemical and biological warfare agent investigations. GAO should report why it has opted to report only on one aspect of what is a broad-based review, and GAO should report why, given the mandate to focus on research and clinical programs, it did not discuss the Committee's work on these matters. Second, DOD was not the only party involved in our external review. The Department of Veterans Affairs, the Department of Health and Human Services, veterans service organizations, and individual veterans and veteran advocates also reviewed the Interim Report and the Final Report.

GAO RESPONSE

Concerning the Committee's observation that DOD was not the only reviewer of its report, we note that DOD publicly endorsed PAC's findings. However, we have added a note that "PAC has asked us to point out that 'DOD was not the only party involved in [its] external review.....VA, HHS, veterans service organizations, and individual veterans and veterans advocates also reviewed [its] Interim and Final Report.' PAC does not provide information on the extent to which these reviewers agreed with its findings or had their comments incorporated." Again, our purpose was not to conduct a review of PAC's activities but to identify and assess the strength of support for conclusions that had been drawn from the available research.

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- Page 70, table IV.1 (as a whole): By reporting incomplete and selective information, this table presents a misleading picture of the Committee's findings.

First, the Committee found: "Although some veterans clearly have service-connected illnesses, current scientific evidence does not support a causal link between the symptoms and illnesses reported today by Gulf War veterans and exposures while in the Gulf region to the following environmental risk factors assessed by the Committee: pesticides, chemical warfare agents, biological warfare agents, vaccines, pyridostigmine bromide, infectious diseases, depleted uranium, oil-well fires and smoke, and petroleum products. Some of these risk factors explain specific, diagnosed illness in a few Gulf War veterans, for example, leishmaniasis has been diagnosed in 32 individuals. Prudence requires further investigation of some areas of uncertainty, such as the long-term effects of low-level exposure to chemical warfare agents and the synergistic effects of exposure to pyridostigmine bromide and other risk factors."

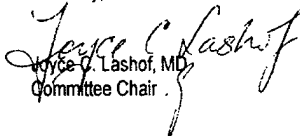
Second, the "reasons" stated, although usually quotes, are incomplete, resulting in bias and/or misrepresentation of the Committee's work. With respect to this table, I have offered the Committee's review for stress, infectious diseases, chemical warfare agents and pesticides, biological warfare agents, and pyridostigmine, above. Although I do not comment directly on those risk factors for which GAO offers no comment, I do not mean this to be construed that I agree with GAO's characterization of the Committee's work.

GAO RESPONSE

Where the Committee has requested that specific changes be made to table IV.1, we have incorporated them (see previous comments).

Thank you again for forwarding the GAO manuscript. In summary, the errors of commission and omission are so serious that the publication of this draft in its current form would do a disservice to the Congress's and President's efforts to address Gulf War veterans' illnesses. In addition to the specific errors relating to the work of the Committee, the draft as a whole is lacking in substantiation and analytic rigor.

Sincerely,

  
Joyce C. Lashof, MD  
Committee Chair

We have presented our detailed responses to the Presidential Advisory Committee in this appendix. We summarize the major points below:

Where the Committee has expressed concerns about citations and cross references to other studies, we have provided additional references and have modified the language in some instances to ensure that other readers will not misconstrue the meaning of our report. We double-checked the information that the Committee challenged and generally found that the data had been correctly stated. Moreover, a careful review of PAC comments indicates that they represent a selective presentation of data that tend to bias the reader's perception of the issues. Therefore, we have not changed the overall thrust of our report.

The Committee also takes issue with our reviews of its conclusions regarding psychological stress, leishmaniasis, and chemical warfare agents.

Regarding stress, PAC states that we ignored its analytical framework, which was to presume that stress occurred and determine whether the types of symptoms and conditions reported by veterans were consistent with exposure to stress. However, the Committee did not provide evidence that stress is an important contributing factor to the "broad range" of illnesses currently being reported by Gulf War veterans. Although we agree that life stress can be associated with a wide array of physical symptoms, the research cited by the Committee largely assesses the relationship between stress and PTSD, which is not a common diagnosis among Gulf War veterans.

Although the Committee notes that scores on PTSD screening questionnaires are higher among Gulf War veterans than among controls, problems are associated with interpreting scores on these scales below the validated cutoff points for PTSD risk. In addition, confirmatory psychiatric interviews to eliminate alternative explanations for elevated PTSD screening scores were not done in most of these studies. Thus, the possibility remains that Gulf War veterans show higher average scores on PTSD screening scales due to other conditions or nonstress-related exposures selectively associated with service. Some studies also modified PTSD screening instruments to make them more applicable to Gulf War veterans; an unintended consequence of this modification is the introduction of information bias (that is, adding questions that selectively affect the scores of Gulf War veterans). Finally, as we note in our report, at least one study that examined the relationship between stress and veterans' physical symptoms in a large sample found none, and in a separate report, its authors noted that, "Although the stress that the

deployed veterans are experiencing can be characterized as substantial, it is being handled unremarkably."<sup>79</sup>

Regarding our evaluation of the conclusion that the likelihood of leishmania infection has diminished as an explanation for widespread illness, the Committee asked, based on the low numbers of cases of leishmaniasis diagnosed in DOD and VA clinical programs, that we justify any continued concern about asymptomatic infection. While there is no fundamental disagreement regarding the available facts or the basic circumstances under which asymptomatic infection is a concern, the Committee's justification for dismissal of leishmania as a risk factor rests heavily on two assumptions: (1) that diagnostic programs have been highly likely to detect the disease, even in the absence of any widely available screening or diagnostic tests and in the presence of nonspecific symptoms, and (2) that the course of various forms of leishmaniasis is well understood by scientists and by the doctors examining the veterans. As discussed in our report, we find these assumptions remain open to question. Moreover, during our exit conference, DOD and VA officials voiced agreement with our concerns in this regard. Insofar as the prevalence of this infection is still unknown and it is impossible to predict which veterans' immune systems will be weakened, it is premature to discard leishmaniasis as a risk factor.

Finally, regarding our evaluation of the Committee's conclusion that low-level chemical exposures are unlikely to be associated with veterans' health conditions, the Committee appears not to contest the fact that laboratory data document specific health effects in animals exposed to one or more organophosphate agents not detectable by the usual clinical tests. While the Committee notes that it recommended additional research in this area, we find it difficult to reconcile the Committee's dismissal of such exposure as an "unlikely" contributor to veterans' health problems with its acknowledgement of an absence of data on an important exposure scenario. Moreover, although the Committee apparently found no data to suggest a problem with low-level exposures, we found some data that do pose concerns. While PAC argues that these studies were done on animals, they are consistent with standard toxicological practice employed by the Environmental Protection Agency and others. The Committee's insistence that such effects be demonstrated in humans appears unreasonable insofar as humans cannot be exposed to toxic substances for experimental research for obvious ethical reasons. Also, comparing occupational or

<sup>79</sup>R. H. Stretch, P. D. Bliese et al. Psychological Health of Gulf War-Era Military Personnel. Military Medicine, vol. 161 (1996), pp. 257-61.

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accidental exposures, such as the Rocky Mountain Arsenal exposures to sarin, to the possible exposures experienced by Gulf War veterans would provide some degree of information, but the value of such information is generally limited because each situation is different. PAC appears to have set an unusually restrictive standard for the evidence that would support any concern in this area.

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# Glossary

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Aflatoxin	Any of several carcinogenic toxic substances that are produced especially in stored agricultural crops, by molds.
Anthrax	An infectious disease of warm-blooded animals caused by a spore-forming bacterium transmissible to man and characterized by external ulcerating nodules or by lesions in the lungs.
Biomarker	A biological indicator, typically of exposure or of susceptibility to illness.
Botulinum	A spore-forming bacterium that secretes a toxin that is the cause of botulism, an acute paralytic disease.
Chemical Agent Resistant Coating	A paintable covering used to protect against chemical and biological attacks.
Decontaminating Solution 2 (DS2)	An extremely corrosive and reactive solution used to decontaminate material of chemical and biological weapons.
Depleted Uranium	A mixture of about 0.2 percent radioactive U-235 and the rest U-238 which is used in armor-piercing shells and armor plating because of its extreme density.
Fibromyalgia	A group of common rheumatic disorders characterized by pain, tenderness and stiffness of muscles, areas of tendon insertions and adjacent soft-tissue structures.
Leishmania	Any of a genus of flagellate protozoans that are parasitic in the tissues of vertebrates. <i>L. tropica</i> is a member of this genus.
Mustard Gas	Chemical warfare agents that blister the skin or any other part of the body they contact. They act on the eyes, mucous membranes, lungs, skin and blood-forming organs. They also damage the respiratory tract when inhaled and cause vomiting and diarrhea when ingested.
Organophosphate-Induced Delayed Neuroathy (OPIDN)	A neurological condition characterized by enlarged axons (long, single nerve cells) and axonal degeneration, caused by exposure to certain chemicals that inhibit cholinesterase, an enzyme important to nervous system functions.
Pyridostigmine Bromide	A drug that was taken by some U.S. troops during the Persian Gulf war to protect them against the nerve agent soman.

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Glossary

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Ricin	A biological warfare agent extracted from the seed of the castor plant. It blocks protein synthesis by altering the RNA, thus killing the cell.
Sarin	An extremely toxic chemical warfare agent that affects the nervous system.
VX	A persistent and extremely lethal nerve agent.

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**Glossary**

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# Related GAO Products

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VA Health Care: Observations on Medical Care Provided to Persian Gulf Veterans (GAO/T-HEHS-97-158, June 19, 1997).

Chemical and Biological Defense: Protection of Critical Overseas Posts and Airfields Remains Largely Unaddressed (GAO/NSIAD-97-9, June 13, 1997).

Operation Desert Storm: Evaluation of the Air Campaign (GAO/NSIAD-97-134, June 12, 1997).

Defense Health Care: Medical Surveillance Has Improved Since the Gulf War, but Results in Bosnia Are Mixed (GAO/NSIAD-97-136, May 13, 1997).

Chemical and Biological Defense: Emphasis Remains Insufficient to Resolve Continuing Problems (GAO/NSIAD-96-103, Mar. 29, 1996).

Operation Desert Storm: Health Concerns of Selected Indiana Persian Gulf War Veterans (GAO/HEHS-95-102, May 16, 1995).

Operation Desert Storm: Potential for Reproductive Dysfunction Is Not Being Adequately Monitored (GAO/T-PEMD-94-31, Aug. 5, 1994).

Operation Desert Storm: Questions Remain on Possible Exposure to Reproductive Toxicants (GAO/PEMD-94-30, Aug. 5, 1994).

Operation Desert Storm: Early Performance Assessment of Bradley and Abrams (GAO/NSIAD-92-94, Jan. 10, 1994).

Operation Desert Storm: Problems With Air Force Medical Readiness (GAO/NSIAD-94-58, Dec. 30, 1993).

Operation Desert Storm: Army Medical Supply Issues (GAO/NSIAD-93-206, Aug. 11, 1993).

Operation Desert Storm: Improvements Required in the Navy's Wartime Medical Care Program (GAO/NSIAD-93-189, July 28, 1993).

Operation Desert Storm: Army Not Adequately Prepared to Deal with Depleted Uranium Contamination (GAO/NSIAD-93-90, Jan. 29, 1993).

Operation Desert Storm: Full Army Medical Capability Not Achieved (GAO/NSIAD-92-175, Aug. 18, 1992).

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Operation Desert Storm: DOD Met Need for Chemical Suits and Masks, but Longer Term Actions Needed (GAO/NSIAD-92-116, Apr. 7, 1992).

Defense Health Care: Efforts to Address Health Effects of the Kuwait Oil Well Fires (GAO/HRD-92-50, Jan. 9, 1992).

Reproductive and Developmental Toxicants: Regulatory Actions Provide Uncertain Protection (GAO/PEMD-92-3, Oct. 2, 1991).

Chemical Warfare: Soldiers Inadequately Equipped and Trained to Conduct Chemical Operations (GAO/NSIAD-91-197, May 29, 1991).

Chemical Protective Suits: No Basis to Question Procuring Agency's Acquisition Strategy (GAO/NSIAD-90-162, May 1, 1990).

Hazardous Materials: DOD Should Eliminate DS2 From Its Inventory of Decontaminants (GAO/NSIAD-90-10, Apr. 25, 1990).

Army Procurement: Unnecessary Restriction on Competition for New Chemical Protective Masks (GAO/NSIAD-88-66, Mar. 2, 1988).

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