

**Scientific Progress in Understanding
Gulf War Veterans' Illnesses:**

Report and Recommendations

**Research Advisory Committee
on Gulf War Veterans' Illnesses**

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The Research Advisory Committee on Gulf War Veterans' Illnesses

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**Executive
Summary**

More than thirteen years after the end of Operation Desert Storm, a substantial proportion of veterans of the 1990-1991 Gulf War continue to experience chronic and often debilitating conditions characterized by persistent headaches, cognitive problems, somatic pain, fatigue, gastrointestinal difficulties, respiratory conditions, and skin abnormalities. Veterans have looked to government officials, scientists, and healthcare providers for answers to their many questions concerning these conditions, often without receiving adequate response or assistance. Research studies conducted since the war have consistently indicated that psychiatric illness, combat experience, or other deployment-related stressors do not explain Gulf War veterans' illnesses in the large majority of ill veterans. Promising scientific advances in recent years have begun to unravel the mysteries of these conditions, providing important new insights into the effects of toxic substances encountered in theater and the physiological processes underlying veterans' illnesses. These advances point the way to continued progress that can be made by a renewed federal research effort focused on a more precise understanding of the chronic effects of exposures encountered in the Gulf War and identification of treatments that improve the health and lives of ill veterans.

The Research Advisory Committee on Gulf War Veterans' Illnesses was established by Congress by Section 104 of Public Law 105-368, and appointed by the Secretary of Veterans Affairs in 2002 to advise the Secretary on research relating to the health consequences of service in the Gulf War. According to its charter, the Committee measures all research on Gulf War veterans' illnesses against a single standard: the potential for that research to improve the health of ill veterans. In the years since the war, thousands of Gulf War veterans have been evaluated and treated by government and private physicians. But the federal research effort has not succeeded in identifying treatments that substantially improve the health of ill veterans. Further, there are no programs in place to evaluate the effectiveness of treatments currently being used or to identify and develop treatments that may hold promise for these conditions.

Many of the veterans who served in the Gulf War were exposed to a variety of potentially toxic substances during their deployment. Among these were several neurotoxins—chemical nerve agents, pills taken to protect veterans from the deadly effects of nerve agents, and multiple types of pesticides—that belong to a single class of compounds that adversely affect the nervous system. A growing body of research now indicates that ill Gulf War veterans differ from healthy controls on objective measures of neurological pathology and impairment. Particularly troubling are findings that Gulf veterans have developed amyotrophic lateral sclerosis (ALS), or Lou Gehrig's disease, at twice the rate of their nondeployed peers. This information parallels recent findings from a large number of animal studies indicating that, contrary to previous assumptions, exposure to nerve agents at levels too low to produce acute symptoms can result in chronic adverse effects on the nervous and immune systems. Additional research has shown that combinations of the types of neurotoxins encountered in the

Persian Gulf theater can work synergistically, producing greater toxicity than would result from the chemicals individually.

This report provides the Committee's key findings and recommendations about the nature and scope of Gulf War veterans' illnesses and the urgent need for treatments that improve the health of ill veterans. It includes findings from the Committee's review of information regarding neurological aspects of veterans' illnesses and their potential linkages to neurotoxic exposures encountered during the Gulf War. Additional recommendations relate to the importance of monitoring the health of veterans over time, the need for additional information regarding the health of veterans' family members, the importance of making full use of existing federal data resources related to Gulf War veterans' health and military service, and the relevance of research in this area to future deployments and homeland security. The report also addresses the overall effectiveness of the federal research effort on Gulf War veterans' illnesses, and recommends the immediate implementation of a targeted research plan focused on treatments and the effects of Gulf War-related exposures.

The conditions affecting Gulf War veterans appear to be complex, involving diverse symptoms associated with multiple organs and physiological systems, possibly as a result of multiple overlapping causes. They present a difficult scientific and administrative challenge for federal agencies responsible for addressing them. Despite recent impressive research breakthroughs, the Committee found, overall, that the federal research effort has not succeeded in answering fundamental questions about Gulf War veterans' illnesses. This has been due, in large part, to lack of effective follow-through in implementing studies that satisfactorily address key research questions, and a continuing focus on stress as the primary explanation for these conditions. Additional progress in addressing Gulf War veterans' illnesses is not likely to come from a haphazard mix of studies. It will require a comprehensive and focused effort, managed to achieve success in answering priority research questions and capitalizing on scientific advances as they emerge. Progress made in recent years by government and non-government researchers indicates that the goal of understanding and treating Gulf War veterans' illnesses is within reach. A renewed effort to effectively address these conditions is particularly important now, given its immediate relevance to current military deployments and homeland security.

Finding 1 A substantial proportion of Gulf War veterans are ill with multisymptom conditions not explained by wartime stress or psychiatric illness. Gulf War veterans experience significantly more chronic and often debilitating symptoms, illnesses, and diagnosed conditions than veterans who did not serve in the Gulf War. Cumulative evidence from multiple studies has demonstrated that Gulf War veterans' illnesses are not adequately explained by deployment stress or wartime trauma and that the large majority of ill veterans have no identifiable psychiatric conditions. Population-based studies consistently indicate that between 26 and 32 percent of Gulf veterans experience a multisymptom

pattern of illness, over and above rates experienced by veterans who did not serve in the Gulf War.

Finding 2 Treatments that improve the health of veterans with Gulf War illnesses are urgently needed. Expert panels and government committees have consistently identified treatments for Gulf War veterans' illnesses to be a top federal research priority. However, no treatments have yet been shown to improve the health of a substantial number of ill veterans, and no programs are in place to identify treatments that may hold promise. The Committee recommends that the Department of Veterans Affairs (VA) immediately establish a comprehensive program specifically tasked with evaluating treatment-related information and research, and developing data and pilot studies as necessary to identify promising candidate treatments for clinical trials for Gulf War veterans' illnesses. This program would employ a multi-faceted approach and should be staffed and managed by professionals with expertise in investigating complex illnesses and in evidence-based methodological approaches to treatment development and evaluation.

The recommended program would include the following components:

- Identification of treatments used by clinicians and veterans for Gulf War veterans' illnesses. Current and previously used treatments can be identified in a variety of ways, including compilation of existing clinical data on treatments administered by VA clinicians and systematic surveys of veterans and clinicians regarding treatments.
- Collection of retrospective and prospective observational data on clinical outcomes associated with treatments used by clinicians, particularly treatments used in VA specialty clinics for Gulf War veterans, and those recommended for use by VA clinical practice guidelines for medically unexplained fatigue and pain.
- Development of a plan for developing and testing innovative but untried treatment strategies. Priority among treatments to be developed and tested should be determined by such considerations as plausibility of benefit based on likely pathophysiological mechanisms of illness, proven effectiveness in treating symptoms or symptom complexes similar to those experienced by Gulf War veterans, and potential for adverse side effects. This plan should include cooperative research with scientists and clinicians outside the VA system with expertise in testing or administering innovative therapies not currently available at VA.
- Development of a general protocol for assessing the evidence on the potential benefit of treatments for Gulf War veterans' illnesses in order to determine which ones appear to be suitable for clinical trials, which require further data development and evaluation, and which appear to hold little potential for benefit.

- Provision of technical assistance and research support to clinicians—both those who currently treat Gulf War veterans' illnesses and those with expertise in administering treatments that may hold promise for these conditions—in developing evidence regarding the effectiveness of treatments.
- Development of guidelines for standardizing essential parameters of Gulf War illness treatment research, including documentation of the definition and measures used to define multisymptom illness and illness subgroups, documentation of the treatment intervention, and measurement of health status before and after the treatment intervention.

Finding 3 **A growing body of research indicates that an important component of Gulf War veterans' illnesses is neurological in character.** Gulf War service is associated with an excess rate of the progressive neurodegenerative condition amyotrophic lateral sclerosis (ALS). In addition, multiple studies have identified elevated rates of neurological symptom complexes in ill Gulf War veterans, as well as objective neurological abnormalities demonstrated using specialized neuroimaging techniques, tests of autonomic nervous system function, and audiovestibular and neuropsychological testing. The Committee recommends that VA expand research efforts that investigate and further characterize neurological abnormalities in ill Gulf War veterans. Specifically, VA should:

- Enlist the expertise of specialists in the neurosciences to develop a comprehensive research initiative capable of examining both neurophysiological and neuropsychological function in symptomatic Gulf War veterans in comparison to healthy controls. This effort should emphasize research protocols capable of identifying specific pathways associated with neurological pathology and include comparisons between subgroups of ill Gulf War veterans characterized by their individual symptom profiles and exposures encountered in theater. Protocols should include evaluation of neurological function under dynamic as well as static conditions.
- Expand research efforts that utilize state-of-the-art neuroimaging technology to better characterize differences between ill Gulf War veterans and comparison groups. This should include studies that follow up and extend previously published findings in Gulf War veterans and other chemically exposed populations using magnetic resonance spectroscopy as well as other imaging techniques suited to study brain cell injury and dysfunction, such as functional magnetic resonance imaging (fMRI), positron-emission tomography (PET), single photon emission tomography (SPECT), 128-channel electroencephalography (EEG), and magnetoencephalography (MEG).
- Develop a comprehensive research strategy designed to evaluate and expand on the growing body of evidence regarding autonomic

dysfunction in ill Gulf War veterans. This effort should give priority to protocols capable of determining which specific aspects of the autonomic regulatory system are affected in symptomatic veterans. As with other studies involving neurological pathology, studies should investigate autonomic function in defined veteran subsets, grouped according to symptom types and exposures encountered during the war.

- Establish a brain bank to collect and maintain samples of autopsy materials from Gulf War veterans for study.

Finding 4 Evidence supports a probable link between exposure to neurotoxins and the development of Gulf War veterans' illnesses. Government reports have described the extent to which Gulf War veterans were exposed to a variety of potentially neurotoxic substances during their deployment to Southwest Asia, including different amounts and combinations of acetylcholinesterase inhibitors (AChEi) such as the nerve agent sarin, pyridostigmine bromide, and carbamate and organophosphate pesticides. Multiple avenues of research have demonstrated that these substances have the potential to cause long-term health effects. Animal research has also indicated that some combinations of Gulf War-related exposures can lead to adverse effects that significantly exceed those resulting from single exposures. Further, epidemiologic studies of Gulf War veterans consistently find that self-reported exposures to these compounds during the war is associated with higher rates of illness. The Committee recommends that the federal government expand research efforts to systematically investigate the chronic effects of exposure to neurotoxins encountered during the Gulf War. Specifically, the Committee recommends that VA:

- Establish a comprehensive research program to investigate persistent and/or delayed effects of exposure to AChEi, including sarin and other nerve agents, at dosages comparable to those that may have been encountered in the Gulf War. Such research should focus on elaboration of the specific physiological pathways involved in possible adverse consequences of these exposures, including those involved in synergistic effects of combinations of neurotoxic exposures.
- Work with scientists with appropriate expertise to comprehensively evaluate the role of differences in genotype and activity levels of enzymes such as paraoxonase, acetylcholinesterase, and butyrylcholinesterase, which are associated with the uptake and metabolism of neurotoxins, in susceptibility to wartime exposures and the development of Gulf War veterans' illnesses.
- Give priority to research studies designed to identify and utilize objective biological markers associated with the effects of exposure to AChEi. Such measures might pertain to effects in the brain or in peripheral areas influenced by acetylcholine such as the neuromuscular system, the gastrointestinal system, and the immune system.

- Give priority to research studies capable of identifying pathways involved in chronic adverse effects of AChEi exposure that may be amenable to treatment interventions.
- Expand VA and collaborative research efforts that capitalize on new technologies capable of identifying low-level residues of exposures, their metabolites, or persistent alterations in metabolism or genetic expression resulting from wartime exposures or associated with chronic unexplained illnesses in Gulf War veterans.
- Analyze data from existing and future epidemiologic studies to reevaluate the association of combinations of neurotoxic exposures with chronic illness in Gulf War veterans.

The Committee recommends that the Department of Defense (DOD):

- Make available to researchers studying Gulf War veterans' illnesses detailed information concerning the locations and dates of incidents involving destruction of chemical targets during and after the Gulf War.
- Continue and expand research efforts that identify possible chronic effects of low-level exposure to sarin and other nerve agents, pesticides, and pyridostigmine bromide, individually and in combination.

Finding 5 Other wartime exposures may also have contributed to Gulf War veterans' illnesses. In addition to neurotoxins, a variety of potentially harmful exposures have been suggested as possible causes or contributors to Gulf War veterans' illnesses. For example, epidemiologic studies have consistently identified significant associations between illness rates and vaccines received in relation to Gulf War deployment. In the coming months, the Committee will investigate in greater detail evidence regarding the potential for additional Gulf War-related exposures to have contributed to veterans' illnesses, including research related to infectious diseases, depleted uranium, oil well fire smoke and other petroleum products, and a more detailed consideration of evidence relating to vaccines.

At this time, the Committee recommends that VA:

- Support research efforts that investigate well-evidenced hypotheses concerning potential linkages between Gulf War veterans' illnesses and wartime exposures, including possible chronic effects of combinations of Gulf War-related exposures.
- Work with federal agencies (Centers for Disease Control and Prevention, National Institutes of Health, Department of Defense) involved in conducting vaccine trials that include administration of anthrax vaccine adsorbed (AVA) to ensure that these trials include follow-up assessments of study subjects a minimum of five years after

inoculation. Such studies should utilize methods and instruments capable of capturing chronic symptoms and cognitive difficulties similar to those experienced by Gulf War veterans.

- Conduct a retrospective cohort study that compares chronic symptoms and diagnosed conditions experienced by veterans who received AVA as part of the military's mandatory anthrax vaccination program to those of a comparable group of veterans who did not receive this vaccine.

Finding 6 The health of Gulf veterans must be carefully monitored to determine if Gulf War service is associated with excess rates of specific diseases, disease-specific deaths, or overall mortality.

The excess rate of ALS identified in Gulf War veterans highlights the need to determine rates of other serious medical conditions in this population. Effects of Gulf War-related exposures on rates of diseases of long latency, including cancer and some neurological conditions, may not become apparent until 10 or more years after deployment. The Committee recommends that rates of medical conditions and disease-specific mortality among Gulf War veterans be regularly assessed and reported. Specifically, the Committee recommends that VA:

- Continue to identify ALS cases among Gulf War veterans, and evaluate the potential role of toxic exposures encountered in theater or after the war in the development or progression of this disease. Publish findings regarding any identified risk factors for ALS in Gulf War veterans, and provide this information to veterans.
- Undertake epidemiologic studies to determine the prevalence of other serious neurological conditions, including multiple sclerosis (MS), Parkinson's disease, and brain cancers, among Gulf War veterans in relation to appropriate comparison groups. Studies should include ascertainment of the number of cases of rare and difficult-to-diagnose neurological conditions that may have clinical similarities to recognized conditions such as ALS, MS, or Parkinson's disease, but are difficult to precisely characterize.
- Analyze and make available mortality data for U.S. Gulf War and nondeployed Gulf War era veterans every 18 months. Data should be analyzed for a wide range of ICD-9 categories and the results made publicly available, electronically and through published reports. Data already available, covering the period 1998 through 2003, should be analyzed and published immediately.
- Utilize troop location information and data collected in VA's National Health Survey of Gulf War-era Veterans and their Families to assess mortality among subcategories of Gulf War veterans grouped by exposure, location, and demographic and military characteristics. Analyses of mortality rates among Gulf War veterans that do not take into account differences in deployment experiences and exposures

could mask even large mortality excesses associated with conditions encountered by a minority of those deployed.

- Regularly monitor information contained in VA clinical and benefit claims data sources and provide annual reports of morbidity and mortality by available diagnostic categories. Age and sex-adjusted rates of hospitalization and benefits claims should be compared between Gulf War and nondeployed Gulf War era veterans, and across military subgroups identifiable through available data.
- Recognizing that assessment of morbidity is difficult for U.S. veterans, for whom health care is not universally available from a single provider, explore the possibility of examining morbidity patterns in allied countries where such data are available. This information may help to identify excesses in chronic diseases before they become apparent using U.S. mortality data or the recommended surveillance activities.
- Where surveillance of clinical or mortality data indicate a possible elevated rate of any condition in Gulf War veterans, undertake appropriate epidemiologic studies to determine the rate of occurrence of that condition among Gulf War veterans and an appropriate comparison group.
- Where a possible excess of any condition is determined, make efforts to identify individuals with that condition among living veterans, especially in situations where early detection and treatment would be beneficial.

Finding 7 Important questions concerning the health of children and other family members of Gulf War veterans remain unanswered. Gulf War veterans have been particularly concerned about possible effects of their wartime service on the health of their families, including the risk of birth defects in children conceived since the war. However, clear information has not been available concerning many unanswered questions in this area. The Committee therefore recommends that VA:

- Accelerate efforts to complete analyses and publish results from Phase III of the National Health Survey of Gulf War-era Veterans and their Families. Reports should contain comprehensive information on the health of veterans' spouses and children, including an accounting of specific diagnosed conditions, symptoms, and symptom complexes. Special effort should be made to assess childhood health problems or abnormalities not apparent at birth, including learning and behavior disorders.
- Analyze data from existing VA studies to evaluate birth defects and other health measures for family members of important veteran subgroups. Analyses should include comparisons between the health of

family members of veterans who are ill and veterans who are well, and comparisons among family members of veterans with different deployment, location, and exposure histories.

- Develop studies with innovative designs to test for excess rates of specific birth defects, such as Goldenhar syndrome, that occur too rarely to address with the types of studies done in the past.
- Continue to query veterans regarding reproductive outcomes and the health of family members in VA's ongoing longitudinal study of Gulf War and nondeployed veterans, and follow up veteran-reported information on birth defects and other health conditions with medical record reviews.
- Issue a public report detailing information and data collected in connection with VA's medical evaluation program for family members of Gulf War veterans.
- Provide clear information to veterans and clinicians concerning what is known about the risk of birth defects related to Gulf War service, and update that information as additional research becomes available.

Finding 8 Progress in understanding Gulf War veterans' illnesses has been hindered by lack of coordination and availability of data resources maintained by the Department of Defense and the Department of Veterans Affairs. The Departments of Defense and Veterans Affairs collect and maintain a large amount of data relevant to the health and military experiences of Gulf War veterans. Progress in understanding Gulf War veterans' illnesses would benefit significantly from researchers making full use of data collected and maintained by different agencies and departments within the federal government. The Committee therefore recommends that VA and DOD:

- Cooperate fully in individual projects requiring linkages between specific Gulf War-associated databases, such as the unit location database and healthcare and benefits data, to facilitate the provision of integrated data resources for research purposes.
- Develop a comprehensive data library that houses and integrates federal military, deployment, and health data resources relevant to service in the Gulf War and the health of Gulf War era veterans. This data library would serve as a central data resource capable of providing usable data for the purposes of conducting research on specific questions regarding Gulf War veterans' illnesses and monitoring the health of Gulf War veterans.
- Make federal data resources relevant to Gulf War veterans' health and military experiences available to qualified government and non-government researchers, and adopt appropriate safeguards for the use of these data.

Finding 9 Research on Gulf War veterans' illnesses has important implications for current and future military deployments and for homeland security. Many issues pertaining to Gulf War-related exposures and government efforts to address Gulf War veterans' illnesses are directly applicable to current and future military deployments. In addition, research on Gulf War veterans' illnesses has immediate relevance to the development of medical countermeasures to protect civilian populations from the threat of chemical terrorist attack.

With respect to the relevance of Gulf War illnesses research to current and future military deployments, the Committee applauds efforts of the Secretary of Veterans Affairs to encourage the Department of Defense to maintain comprehensive records of deployment-related health information, including receipt of vaccines, in connection with current military deployments. The Committee further recommends that:

- DOD fully implement the military assessment programs mandated in 1997 by Public Law 105-85, Section 765 (10 U.S.C. §1074f (1997)), which directs DOD to conduct detailed medical examinations of all military personnel before and immediately after deployment to hostile areas, including the collection and storage of blood samples taken before and after deployment.
- DOD take steps to improve record keeping and exposure assessments related to military deployments.
- DOD reassess policies regarding the use of pyridostigmine bromide as a prophylactic measure against the possible effects of nerve agents. This assessment should include a comprehensive review of scientific studies relating to adverse effects of pyridostigmine bromide in combination with other exposures, and revisiting policies concerning the circumstances and decisions that govern orders for the use of pyridostigmine bromide.
- DOD and VA work cooperatively to immediately share information related to current military deployments, including health experiences and exposures in theater.
- DOD and VA continue to work cooperatively to develop and implement a unified health data system that will include all health information of personnel through their military service and transition into the VA healthcare system.

With respect to the relevance of Gulf War illnesses research to preparations against chemical terrorism, the Committee recommends that Congress:

- Establish a comprehensive medical chemical defense research program within the NIH counterterrorism research agenda, and provide adequate funding to field effective medical countermeasures. Enlist in this effort

the capabilities of relevant agencies, including the Department of Defense and the Department of Veterans Affairs.

- Expand funding for research programs sponsored by the Department of Defense relevant to chemical defense measures. In particular, continue and expand support for research programs that have provided important information regarding the chronic health effects of sarin and other chemical agents.

Finding 10 Further progress in understanding and treating Gulf War veterans' illnesses requires federal research programs that are properly focused, well-managed, and adequately funded.

Overall progress in addressing Gulf War veterans' illnesses has been delayed by the lack of a well-coordinated federal research effort managed to successfully address key research priorities, and by an ongoing emphasis on studies that focus on psychological stress as the primary explanation for these conditions. The Department of Defense no longer supports new research on Gulf War veterans' illnesses, resulting in a dramatic decrease in federal funding in this area in recent years. Reduced support for this research is of particular concern now, as recent breakthroughs provide new progress in understanding veterans' illnesses.

The Committee therefore recommends that VA:

- Develop a comprehensive federal research plan to address Gulf War veterans' illnesses in conjunction with other participants in the Research Subcommittee of the Deployment Health Working Group and with the Research Advisory Committee on Gulf War Veterans' Illnesses. The plan should address priority research topics identified in this and future Committee reports. It should also utilize scientific resources and funding mechanisms available at each federal agency in order to enlist government and non-government scientific experts most capable of undertaking research projects that can best address priority topics.
- In the context of the comprehensive federal research plan, adopt a strategic VA research program that identifies and addresses key research questions regarding the nature, causes, and treatments for Gulf War veterans' illnesses, utilizing research solicitations that address specific priority Gulf War illnesses research topics.
- Maintain a substantial research funding commitment to address the health consequences of Gulf War deployment until specific treatments and causes for these conditions are identified. Specifically, VA should allocate not less than 15 million dollars in each of the next four years in support of a comprehensive and well-managed research portfolio.
- Work with leading scientists—both those within VA and those not affiliated with VA—to develop comprehensive research protocols most capable of addressing priority Gulf War illnesses research questions.

- Establish an effective management strategy for the VA Gulf War illnesses research portfolio to ensure that studies capable of addressing priority research questions are satisfactorily developed and completed. The program should be directed by a doctoral-level scientist with appropriate expertise in research directly relevant to Gulf War veterans' illnesses.
- Adopt a mechanism for reviewing and funding Gulf War illnesses research proposals that takes into account the relevance of proposed projects to identified Gulf War illnesses research priorities, in addition to the scientific merit of the proposed research. Merit review panels should include scientists familiar with current research on Gulf War veterans' illnesses and established research priorities.
- Allocate a significant proportion of Gulf War illnesses research funding to treatment research, including specific annual allocations for the recommended treatment development program and pilot studies, and additional funding for small and large clinical trials, as scientifically appropriate.
- Give funding priority to studies that pursue significant research breakthroughs, such as those identified throughout this report. Do *not* fund studies in areas that accumulated research has found not to be useful in understanding the unexplained illnesses affecting Gulf War veterans, unless such proposals can be justified by new evidence or innovative hypotheses. For example, although psychiatric conditions such as posttraumatic stress disorder are appropriate topics for deployment health research in general, research proposals on Gulf War veterans' illnesses should not be funded if their principal focus is on psychological stress as the primary cause of these conditions.
- In conjunction with the Committee, regularly review progress on the objectives established for the Gulf War illnesses research program, to determine which have been adequately addressed, which should be revised, and which require additional follow-through with new and/or more specific funding announcements.

The Committee recommends that Congress:

- Set a national goal to develop treatments for the chronic multi-symptom illnesses affecting Gulf War veterans within five years.
- Establish line-item funding within the appropriations budgets of the appropriate federal departments that provides a total annual federal Gulf War illnesses research commitment adequate to execute the comprehensive Gulf War illnesses research plan, and in no event less than 45 million dollars, consistent with the annual funding levels invested in Gulf War illnesses research between 1999 and 2001.

- Designate that 15 million dollars of the annual federal Gulf War illnesses research funding be specifically added to VA's current research and development budget in support of the recommended comprehensive Gulf War illnesses research program. The balance should be provided to the Departments of Defense and Health and Human Services, as appropriate for the specific projects to be funded and, in particular, for research conducted by non-government research scientists on a competitive basis.

Introduction **Unexplained illnesses in the wake of Desert Storm.** Veterans who served in the 1990-1991 Persian Gulf War have a compelling story. That story conveys the tragedy and triumph of war and, for some, a long struggle with unexplained and often debilitating health problems experienced in the years since the war. Veterans have looked to government officials, scientists, and healthcare providers for answers to the many questions they have regarding the nature, causes, and treatments for these conditions, often without receiving adequate response or assistance. At the writing of this report in 2004, this story is ongoing, having begun in the deserts of Southwest Asia 14 years ago.

In August of 1990, the Iraqi army invaded the small neighboring nation of Kuwait, triggering an immediate response from the United States and an international coalition of allied countries organized in opposition to Iraq's aggression. Within weeks, Operation Desert Shield, the massive buildup and positioning of Coalition troops in the region, was underway. Operation Desert Storm began with the first Coalition air strikes on January 16, 1991, and continued with the start of the ground war on February 24, 1991. The war was swiftly brought to an end by a decisive Coalition victory. Three days into the ground war the liberation of Kuwait was achieved, as Coalition tanks moved triumphantly into Kuwait City. A ceasefire was declared the following day—just four days after the initiation of the ground war and six weeks after air strikes had begun. Coalition forces had succeeded more completely, more rapidly, and with fewer casualties than anyone had expected or hoped for.

American troops returned home to parades and accolades, honored for their success in accomplishing their mission of liberating Kuwait. In the months after their return, however, stories began to circulate from different units that some who had served in the Persian Gulf theater of operations were now experiencing unexplained health problems. Some of these difficulties were said to have begun during deployment or soon after veterans had returned home, but had not resolved with time. Other problems had not become apparent for months. The symptoms reported by different individuals varied in type and severity, ranging from somewhat troubling but chronic muscle pain and skin rashes to more serious presentations involving a complex of debilitating problems including severe headaches, joint pain, difficulties with balance, memory, and cognition, and chronic respiratory and gastrointestinal conditions. As time went on, similar problems were reported by veterans in different units and branches of service, different areas of the United States, and by veterans from other Coalition countries.

What had caused these health difficulties? Had the many chemical alarms sounded in theater signaled that veterans had been exposed to some of the same chemical agents the Iraqi regime had used against Iran and against its own citizens? Had exposure to the smoke from hundreds of oil well fires set in the closing days of the ground war contributed to these conditions? Initial impressions of the nature and causes of these conditions varied widely, as did reports of the magnitude of the problem. Almost

from the beginning, different camps developed in which veterans, scientists, and government officials variously promoted different causes and explanations for Gulf War veterans' illnesses. The central question in this controversy was whether veterans were suffering from the chronic effects of one or more exposures experienced during their deployment or if these conditions were the consequence of the stress of deployment and the trauma of war.

Proponents of the stress theory maintained that military populations often experience unexplained symptoms after deployment to hostile areas, and that an element common to all deployments is the extreme psychological stress and trauma associated with a war zone. The suggestion was that the health experience of Gulf War veterans was no different from that of prior wars and that the medical problems of Gulf War veterans were the expected consequence of service in a hostile area. Advocates of the view that Gulf War-related exposures had caused these conditions pointed out that a relatively low proportion of military personnel had experienced serious psychological stress and trauma during the Gulf War, and that post-war psychiatric conditions were actually less prevalent in Gulf veterans than in veterans of earlier wars. They identified numerous wartime exposures that could plausibly have led to the types of health problems affecting veterans.

The controversy and challenges of understanding Gulf War veterans' illnesses have been reflected in the findings and conclusions of numerous Congressional reports, special government panels, and scientific review committees appointed to look into this problem.^{130,131,134,137,221,240,241,305,346-348} These reports have unanimously acknowledged the seriousness of the unexplained symptoms affecting Gulf War veterans, but have differed in their conclusions regarding the probable nature and causes of these conditions. One general theme that has emerged from these reports, however, is that progress in understanding Gulf War-related health problems has been severely hindered by a lack of information. All have pointed to the need for improved monitoring of the health of military personnel and exposures during wartime, and improved recordkeeping, to provide a better understanding of the health consequences of future deployments. Another conclusion reached by several government panels is that Gulf War veterans do not appear to be affected by a single syndrome unique to the Gulf War, but rather a mix of multisymptom conditions for which no singular cause or diagnostic test has been clearly identified. The other common thread emerging from earlier reports has been the difficulty in drawing clear conclusions regarding the nature of Gulf War veterans' illnesses due to the lack of scientific information regarding the long-term health effects of many of the exposures encountered in the Persian Gulf theater.

The one indisputable fact is that, after the many conclusions and recommendations put forward by special committees and panels, and research expenditures of hundreds of millions of dollars to investigate this problem, Gulf War veterans remain ill. These veterans deployed to the

Persian Gulf theater as healthy soldiers, airmen, sailors, and marines, but returned with unexplained health problems and unanswered questions, which continue thirteen years after Desert Storm.

Research Advisory Committee on Gulf War Veterans' Illnesses.

The Research Advisory Committee on Gulf War Veterans' Illnesses was established by Congress in 1998 by Section 104 of Public Law 105-368, in order to provide advice to the Secretary of Veterans Affairs on "proposed research studies, research plans, or research strategies relating to the health consequences of military service in the Southwest Asia theater of operations during the Persian Gulf War" (38 U.S.C. §527(b)(1998)). Although the legislation required that the Committee be established by 1999, no action was taken until Secretary of Veterans Affairs Anthony J. Principi appointed the Committee in January, 2002. According to its charter, the Committee is required to review "all relevant research, investigations, and processes for funding research" as well as "all proposed research plans, initiatives, procurements, grant programs, and other activities in support of research projects on Gulf War-associated illnesses and assess the individual research projects and the overall effectiveness in answering central questions on the nature, causes, and treatments for Gulf War-associated illnesses" (Appendix C).

The Committee consists of eleven members that include veterans, physicians, and scientists (Appendix A), and is supported in its work by one consultant and a small staff. A six-member expert advisory panel named by the Secretary to assist the Committee (Appendix B) is consulted informally on specific scientific questions, and the Committee regularly seeks the advice and input of other scientists and professionals. In accordance with its charter, the Committee measures all research on Gulf War veterans' illnesses against a single standard: the potential for the research to improve the health of ill veterans.

Committee meetings have been held three times per year and have primarily consisted of briefings and scientific presentations on research related to possible health consequences of Gulf War service and exposures, and on governmental programs and activities related to research on Gulf veterans' illnesses. The meetings have often served as symposia on specific topics related to Gulf veterans' health, typically including presentations by several scientists on a specific research topic, followed by questions and discussions among Committee members and visiting scientists. Government officials associated with medical research programs are also invited to participate. All Committee meetings are open and include time for members of the public to provide comments and suggestions on matters relating to Gulf War veterans' illnesses.

In June, 2002, the Committee issued an Interim Report, containing preliminary findings and recommendations based on information reviewed by Committee members in the first several months of their work. This interim report signaled the Committee's commitment to a reappraisal of research on Gulf War veterans' illnesses, in accordance with the

Secretary's call to approach these complex issues from a fresh perspective, and to target research opportunities capable of producing maximum progress toward improving veterans' health. Specifically, the Committee found that Gulf War illnesses constitute a serious health problem that affects a significant proportion of veterans who served in the 1990-1991 Gulf War, that these conditions cannot be adequately explained by stress or psychological factors, and that a growing body of evidence indicates that an important component of these conditions appears to be neurological in character.

Scientific progress in understanding Gulf War veterans' illnesses. In the time since the Committee's Interim Report was issued, important scientific developments have taken place that confirm the report's preliminary findings. A flood of new studies from government and non-government researchers has begun to unravel the complex physiological processes underlying Gulf War illnesses and shed light on the potential for Gulf War-related exposures to produce long-term adverse health effects. Taken together, this research lays the groundwork for a new era in understanding and addressing Gulf War veterans' illnesses. Pursuit of these findings represents an important scientific opportunity to explain the mechanisms underlying veterans' conditions, potentially pointing the way to development of medical treatments.

In recent years, studies have provided additional objective evidence of neurological impairment and injury and altered autonomic function in ill Gulf War veterans. During the same period, numerous animal studies have found that low-dose exposure to sarin is associated with chronic neurological and immunological effects. Such findings dispel previous long-held assumptions that nerve agent exposures too low to produce immediate symptoms cannot produce long-term health problems. Additional recent studies have provided further evidence that the majority of symptomatic Gulf War veterans have no diagnosable psychiatric conditions and shed new light on the long-term prognosis of Gulf War illnesses and the health of veterans' children. This new research calls into question earlier perceptions regarding Gulf War-related illnesses and exposures and mandates fundamentally different conclusions from those reached by previous review panels.

The work of the Committee is ongoing. This report addresses the nature and scope of Gulf War illnesses, and focuses on the urgent need to develop treatments for these conditions. It also reviews research evidence related to neurological aspects of veterans' illnesses and the possible contribution of neurotoxic exposures. Additional recommendations relate to the need to monitor the health of Gulf veterans, including the importance of making full use of government databases containing information on the health of Gulf War veterans. Preliminary findings are presented regarding the potential for other deployment-related exposures, including vaccines, to have contributed to Gulf War veterans' illnesses, and on the need for additional information on birth defects and the health of veterans' family members. Future reports will expand on preliminary findings in these

areas, and will review the scientific evidence related to possible health effects of additional exposures encountered by military personnel during the Gulf War such as depleted uranium, infectious diseases, smoke from oil fires, and other potentially toxic substances. Additional topics to be addressed in future Committee meetings and reports will include a more detailed examination of medically diagnosed conditions affecting Gulf War veterans, treatments used for Gulf War veterans' illnesses, and parallels between Gulf War illnesses and conditions found in the general population.

Administrative challenges in addressing Gulf War Veterans' illnesses. While recent scientific progress in understanding Gulf War veterans' illnesses is encouraging, further advances in addressing these conditions depends on the commitment and sustained support of federal agencies responsible for the health of military and veteran populations. Despite the presence since 1995 of a federal interagency working group that identified research priorities in this area, a coordinated and focused federal research program that asks and answers the central outstanding questions regarding Gulf War veterans' illnesses has not yet been achieved. In recent years, prospects for a coordinated federal Gulf War illnesses research effort have been overtaken by events. The Department of Defense (DOD) had historically provided the bulk of funding for Gulf War illnesses research, and many of the recent scientific breakthroughs came from studies funded several years ago by DOD. More recently, however, DOD has shifted its focus from research on Gulf War veterans' unexplained illnesses to deployment health protective measures related to current and future military deployments. As a result, federal funding in this area has dramatically declined, and the Department of Veterans Affairs (VA) is now the only federal agency sponsoring new research on Gulf War veterans' illnesses.

In response to the Committee's Interim Report, the Department of Veterans Affairs announced a renewed commitment to Gulf War illnesses research. In October, 2002, VA announced that it was doubling Gulf War research funding by making available up to 20 million dollars in fiscal year 2004 for research related to Gulf War veterans' illnesses and other deployment health concerns.³²⁸ Subsequently, several research activities responsive to the Committee's interim recommendations were undertaken, but the promise of a major initiative remained unrealized. In February, 2004, the Secretary of Veterans Affairs directed VA's Office of Research and Development to work directly with the Committee to develop an effective program capable of making significant progress. The Committee recommended a targeted approach to Gulf War illnesses research that directs resources toward areas of highest priority and greatest promise. At the writing of this report, plans to initiate such a program have just begun. The Committee will continue to review VA's progress in developing a well-planned and comprehensive research effort to address Gulf War veterans' illnesses. Such a program is sorely needed and long overdue, as a significant effort is required to achieve the goal of utilizing the best science to improve the health of ill Gulf War veterans.

Finding 1
A substantial proportion of Gulf War veterans are ill with multisymptom conditions not explained by wartime stress or psychiatric illness.

The health problems reported by Gulf War veterans since the end of Desert Storm have posed a complex and frustrating challenge for veterans who are ill, as well as for clinicians, researchers, and government agencies charged with understanding and addressing these conditions. Epidemiologic research, the study of patterns of health and disease in populations, is often the first scientific approach taken in understanding unexplained health problems. Since the Gulf War, population-based epidemiologic studies have investigated the health status of many different groups of Gulf War veterans, including veterans from different branches of service, veterans from different countries and states, and veterans who served in different areas of theater.^{24,51,85,94,97,138,139,158,237,285,293,349} Despite the diversity of research approaches and groups studied, a number of common threads have emerged from these investigations, providing insight to key questions about the characteristics and prevalence of Gulf War veterans' illnesses.

Epidemiologic findings regarding the nature and prevalence of Gulf War veterans' illnesses. A number of epidemiologic studies have compared hospitalization and mortality rates of Gulf War veterans to those of era veterans who did not deploy to the Persian Gulf region (nondeployed veterans). The earliest studies comparing hospitalization rates between Gulf War and nondeployed veterans utilized data from military hospitals and found no significant differences between the two groups.^{96,176} These studies were somewhat limited in scope, since they did not include veterans no longer serving in the military. Early comparisons between Gulf War and nondeployed veterans may also have been affected to some extent by the "healthy warrior effect"¹⁰² that arises from the fact that personnel who meet fitness qualifications required for deployment to war tend to be healthier and less likely to require hospitalization than personnel who do not deploy.¹⁷⁶ In later hospitalization studies, Gulf War veterans have been shown to have proportionally higher rates of hospitalization in broad categories such as musculoskeletal disorders,³⁴ digestive diseases, respiratory diseases, symptoms, signs and ill-defined conditions, and injuries and poisoning,⁹⁹ and for specific diagnoses that include gastroenteritis and colitis, asthma, fractures, and fibromyalgia.^{99,274}

Mortality studies in the United States and United Kingdom have found Gulf War veterans to have significantly higher death rates due to accidents and injuries than nondeployed Gulf War era veterans,^{153,154,192,301} but no differences in death rates due to specific diseases. Research studies have not provided empirical explanations for the excess number of deaths due to motor vehicle accidents among Gulf War veterans.²⁹ Proposed explanations have included higher rates of PTSD or depressive disorders associated with Gulf War service,¹⁵³ an increase in risk-taking behavior following veterans' return from the war¹⁵⁴ and Gulf War-associated neurological damage leading to impaired attention and driving ability.¹⁰²

It will be important to follow Gulf War veterans for many years in order to monitor deaths due to diseases with long latency periods, such as cancer and neurodegenerative diseases. At this time, however, epidemiologic

studies evaluating hospitalization and mortality rates have identified only limited distinctions between Gulf War and nondeployed veterans. These differences are considerably less striking than those identified in a large number of epidemiologic studies that have evaluated rates of post-Gulf War health problems not generally associated with either hospitalization or death. The most prominent and consistent finding to emerge from population-based studies of Gulf War era veterans is that veterans who served in the Gulf War experience a wide range of symptoms at significantly higher rates than their contemporaries who did not serve in the Gulf War. Representative symptoms reported by Gulf and non-Gulf veterans from a survey of over 20,000 U.S. veterans are shown in Table 1.

Table 1. Proportion of U.S. Gulf War-era Veterans Reporting Symptoms in a National Survey

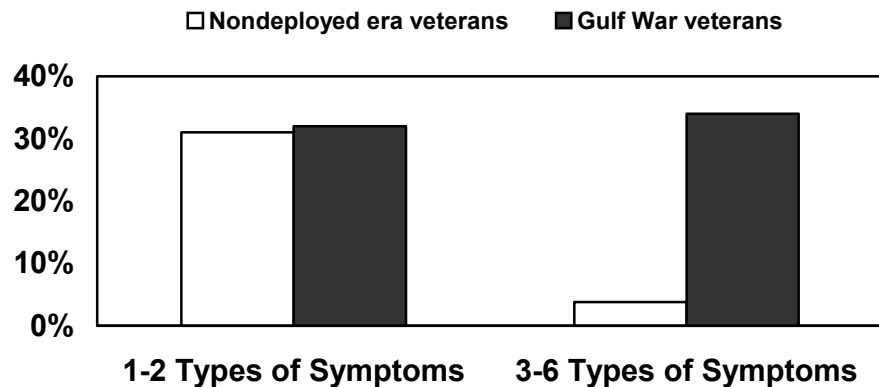
	Gulf War Veterans	Non-Gulf Veterans
Headache	54%	37%
Joint pain	45%	27%
Fatigue	38%	15%
Depressed	36%	22%
Difficulty concentrating	35%	13%
Muscle pain	33%	17%
Diarrhea	31%	15%
Skin rash	29%	13%
Coughing	24%	14%
Shortness of breath	24%	11%
Hair loss	23%	12%
Abdominal pain	23%	12%
Dizziness	22%	10%
Difficulty with speech	10%	3%
Burning semen	7%	1%

Source: National Health Survey of Gulf War-era Veterans and their Families¹⁵⁸

As shown, individual symptoms experienced by Gulf War veterans are not unique in that they are also reported by veterans in non-Gulf comparison groups, albeit at lower rates. The observation that veterans who did not serve in the Gulf War report symptoms is not unexpected, since it has long been known that some level of symptomatology is found in any population group.^{178,352} But Gulf War veterans report symptoms in patterns that are distinct from other veterans and from the general population.^{286,287} Specifically, Gulf War veterans experience a greater number of symptoms than comparison groups, more severe symptoms than comparison groups, and are more likely to report multiple different types of symptoms simultaneously.^{85,285} In contrast to the occasional headache or digestive problem or joint pains that might afflict anyone from time to time, it is not uncommon for Gulf veterans to experience severe headaches and joint pain and chronic diarrhea all at the same time, perhaps in connection with dizziness, memory problems, fatigue, and skin rashes, and for these problems to have persisted over many years.

Figure 1 shows the proportion of Gulf War and nondeployed veterans who reported having multiple or moderate-to-severe symptoms in six different symptom domains (fatigue symptoms, pain symptoms, neurocognitive symptoms, respiratory symptoms, gastrointestinal symptoms, and skin symptoms) from a population-based study of Kansas Gulf War era veterans.²⁸⁵ As shown, a similar proportion of Gulf and non-Gulf veterans reported a relatively low level of symptoms—that is, symptoms in just one or two of the six defined symptom groups. However, over 30 percent of Gulf veterans reported having moderate-to-severe symptoms in three or more of the symptom domains, compared to less than five percent of the comparison group. So, while individual symptoms may not be uniquely associated with Gulf War service, the pattern of symptoms in Gulf War veterans is distinct, in terms of symptom frequency, severity, duration, and the occurrence of multiple symptom types together.

Figure 1. Proportion of Gulf War era Veterans Reporting Symptoms in Six Symptom Domains²⁸⁵



In addition to undiagnosed symptoms, population-based studies have found that Gulf veterans have significantly higher rates of some types of diagnosed medical conditions than non-Gulf veterans. Most prominently, a 2003 epidemiologic study from the Department of Veterans Affairs (VA) found that Gulf veterans have developed a serious neurodegenerative disease, amyotrophic lateral sclerosis, at twice the rate of nondeployed era veterans in the years since the war.¹¹⁷ Moreover, three population-based studies have provided information on rates of other medical and psychiatric conditions for which veterans report being diagnosed, as shown in Table 2.^{98,285,349} Of note, significantly more Gulf veterans report being diagnosed with migraine headaches and with skin, gastrointestinal, and respiratory conditions than comparison groups, as well as depression and post-traumatic stress disorder. However, Gulf War service has generally not been associated with increases in most age-related chronic conditions such as cancer and diabetes.^{158,191,285}

Table 2. Diagnosed Conditions Reported at Significantly Higher Rates by Gulf Veterans than Nondeployed Veterans

	Proportion of Gulf Veterans Reporting Condition
Skin conditions ^{98,285,349}	20-21%
Migraines ^{98,285,349}	7-18%
Stomach or intestinal conditions ²⁸⁵	15%
Depression ^{98,285}	8-12%
Bronchitis ^{98,285,349}	7-10%
Arthritis ^{98,285,349}	6-11%
Hypertension ^{98,349}	8-9%
Asthma ^{285,349}	4-7%
Posttraumatic stress disorder ^{98,285}	3-6%

Population-based studies have also consistently identified excess rates of symptom-defined diagnoses such as chronic fatigue syndrome (CFS), fibromyalgia, and multiple chemical sensitivity among Gulf War veterans in comparison to both nondeployed veterans and the general population.^{98,138,160,243,248,285,349} For example, symptom-based estimates of the prevalence of CFS have ranged from two to five percent among Gulf War veterans, significantly higher than estimates of zero to 1.8 percent in nondeployed veterans and actual CFS rates of 0.2 to 0.4 percent found in the general population.^{145,250}

Relationship of veterans' illnesses to Gulf War service. In light of the large body of evidence demonstrating excess morbidity in Gulf War veterans, there is now general consensus among researchers and government officials that Gulf War veterans are affected by an abnormally high rate of chronic multisymptom illnesses. Some reports, however, have suggested that these conditions may not result from experiences or exposures specific to the Gulf War, since unexplained symptoms have occurred after other wars and are also observed in civilians who have experienced traumatic events.^{54,86,129,148,292} Excess rates of both medical and psychiatric conditions have been observed in veterans after service in many previous conflicts, including conditions resulting from psychological trauma, infectious diseases, and chemical and radiological exposures.

Several lines of evidence, however, have indicated that Gulf War veterans' illnesses are the result of experiences specific to the Gulf War, rather than a nonspecific result of deployment-related stress or trauma. For example, many epidemiologic studies have identified significant associations between rates of multisymptom illness and specific exposures that veterans report during the Gulf War, including smoke from oil well fires, receipt of multiple vaccinations, hearing chemical alarms, ingestion of pyridostigmine bromide, and use of pesticides.^{52,107,138,222,244,349} Despite the large number of findings relating veterans' symptoms to wartime

exposures, this information is generally considered to be inconclusive, due to limitations in veterans' knowledge and recollection of what they might have been exposed to during the war, and at what levels. In general, the lack of more objective government data on veterans' exposures in the Persian Gulf theater has required investigators to rely on veterans' self-reported experiences and exposures in order to identify possible linkages between individual exposures and Gulf War veterans' illnesses.

Other types of evidence relating veterans' illnesses to events specific to the Gulf War come from studies of Kansas and British veterans. A 2000 study of Kansas veterans found rates of Gulf War illness to differ significantly by the locations and time periods in which veterans served during the war.²⁸⁵ Gulf War illness rates were lowest (21%) among veterans who served primarily on board ship, higher in veterans who served on land but remained in support areas (31%), and highest (42%) in veterans who entered Iraq or Kuwait, countries in which the ground war and Coalition air strikes took place. Illness rates also varied with the time periods veterans were present in theater, with the lowest rate (9%) among veterans who departed the region before the start of the air war in January, 1991, and the highest rate (43%) among veterans who were still in theater five months after the cease-fire. Differences in illness rates by location and time period indicate that veterans' illnesses are linked to specific experiences during deployment, evidence that is independent of veterans' recollections concerning specific exposures.

Additional evidence that links Gulf War veterans' symptoms to experiences specific to the Gulf War comes from a large British study that found high rates of multisymptom illness in Gulf War veterans, but not in veterans who served in the Bosnian conflict.^{121,349} Striking differences between the health of the two groups were first described in 1999 and have been sustained over time, as reported in a study that reassessed the health of both veteran groups after a four-year follow-up period.¹²² Such clear and consistent differences between the health of Gulf and Bosnia veterans evaluated in a comparable manner are another important indication that Gulf veterans' illnesses result not from a generalized reaction to the stress of deployment but from experiences specific to service in the Persian Gulf theater.

Deployment stress does not account for the unexplained conditions affecting Gulf War veterans. Early reports suggested that the unexplained illnesses reported by Gulf War veterans may have resulted primarily from wartime stress.^{179,240,241} As additional research has become available, however, it has become evident that these conditions cannot be adequately explained by deployment stress, wartime trauma, or psychiatric diagnoses such as posttraumatic stress disorder (PTSD). This is not surprising, given the general circumstances of the Gulf War. The war was short, requiring only four days of ground combat to achieve a decisive victory. Casualty rates were very low, and the vast majority of veterans were never in combat areas and did not witness any deaths during deployment.^{158,222,285}

Some individuals did experience traumatic events during the Gulf War, and now experience psychological problems as a result. Data from multiple sources, however, indicate that, overall, PTSD rates are lower in Gulf veterans than in veterans of previous wars,^{199,357} and are more similar to PTSD rates in the general population.^{173,360,362} Only a fraction of veterans reporting chronic health problems since Desert Storm suffer from PTSD. For example, VA has reported that less than four percent of veterans examined in its Gulf War registry have either a primary or secondary diagnosis of PTSD.³³⁴ Similarly, a RAND report commissioned by the Department of Defense to review the scientific evidence concerning stress and Gulf War illnesses concluded that overall rates of PTSD are low in Gulf War veterans, and identified little evidence linking wartime stressors to medical symptoms.¹⁹⁹

Research spanning several decades has described the complex relationship between medical and psychiatric symptoms and illness.¹⁹⁹ Studies of veterans from different wars have consistently found those with PTSD to have more symptomatic complaints than those without PTSD.^{42,115,175,354,360} The reverse is also true. Individuals with chronic medical conditions such as cancer and multiple sclerosis are known to have more psychiatric illnesses than those who are not ill.^{119,230,284,296} Evaluating the relationship between medical and psychiatric illness, especially in conditions identified primarily by symptoms, can be complicated by the fact that some symptoms, such as fatigue, cognitive difficulties, and depression can result from physical causes (such as head injuries or the sequelae of toxic exposures) or from psychological causes (such as traumatic experiences, or the stress of chronic illness).

Unfortunately, early studies that evaluated the health of Gulf veterans often did not use research methods capable of distinguishing between physical and psychologically-based symptoms, sometimes leading to erroneous conclusions about medical and psychiatric aspects of Gulf War illnesses. For example, early studies often relied on psychometric screening tests to estimate the prevalence of PTSD and “stress-related symptoms” in ill Gulf War veterans, rather than more definitive psychiatric assessments using diagnostic measures such as the Clinician Administered PTSD Scale (CAPS).^{32,101,199} Psychometric tests used in such studies were typically designed to screen for PTSD in individuals known to have experienced traumatic events. These screening tests identify PTSD cases based on the number of problems veterans endorse from a list of nonspecific symptoms—including such problems as fatigue, difficulty concentrating, and night sweats—that can be associated with many types of medical conditions. As a result, psychometric screening tests can erroneously identify veterans with multisymptom medical conditions as having PTSD, without reference to whether they had experienced traumatic events during their service in the Gulf War.

More recent studies, using more sophisticated evaluation and analytic approaches, have found that Gulf veterans experience significantly higher rates of unexplained symptoms than non-Gulf veterans, even after

controlling for the effects of wartime stressors and psychiatric diagnoses.^{180,244,297,357,360} For example, a New Jersey study found similar levels of physical impairment in Gulf War veterans with and without comorbid psychiatric conditions and concluded that reduced levels of physical functioning in Gulf veterans cannot be attributed to psychiatric illness.²⁹⁷ A 1998 study of three groups of Army veterans controlled both for the effects of in-theater psychological stressors and for PTSD, and found excess symptomatology in Gulf veterans associated with a variety of war zone exposures.²⁴⁴ A related study determined that two-thirds of the most symptomatic veterans had no axis I psychiatric disorders.³⁶⁰ In a larger follow-up study, stratified multivariate analyses determined that, among veterans with low levels of psychological distress, illness was most strongly associated with self-reported exposure to oil fire smoke and ingestion of more than 21 anti-nerve gas pills.³⁶¹ More recently, a study of British veterans sponsored by the U.S. Department of Defense found that about 24 percent of the most disabled Gulf veterans had identifiable psychiatric disorders, a proportion similar to that found in a comparison group of disabled veterans who had not served in the Gulf War. Seventy-six percent of ill Gulf veterans had no identifiable psychiatric condition, leading investigators to conclude that “alternative explanations for the persistent ill health in Gulf War veterans are needed.”¹⁴¹

How many veterans are affected by Gulf War-related health problems? The question of the number of veterans with unexplained health problems is of key importance to veterans, government officials, and healthcare providers. As of May, 2004, over 179,000 Gulf veterans, or 30 percent of eligible veterans who served in the Persian Gulf conflict, had been determined by VA to have a service-connected disability.³²⁹ This figure includes the total number of veterans with approved claims for any disability connected to their military service, not only claims specifically for undiagnosed conditions linked to service in Desert Storm. Government and media reports have frequently reported that about 100,000 of the nearly 700,000 U.S. Gulf veterans, or 14 percent, are experiencing Gulf War-related health problems. This figure appears to be based on enrollment in government registries rather than on information from scientific studies. As shown by the prevalence figures listed in Table 3, research-based estimates of the proportion of veterans who are ill vary widely from study to study, depending on how the “Gulf War multisymptom illness” complex is defined.

Because symptoms reported by Gulf War veterans also occur at lower rates among individuals who did not serve in the Gulf War, evaluation of the burden of illness associated with Gulf War service should be based on the *excess* rate of multisymptom illness in Gulf veterans—that is, the level above that expected had veterans not deployed to the Persian Gulf theater. Such information is readily available from population-based studies that have compared the rates of multisymptom illness in Gulf War veterans to rates in nondeployed era veterans.

Table 3. Prevalence Estimates of Multisymptom Illness in Gulf and Non-Gulf Veterans

Group Studied	Case Definition Used	Prevalence in Gulf War Veterans	Prevalence in Non-Gulf Veterans	Excess Illness in Gulf Veterans
Pennsylvania Air Guard ⁸⁵	CMI	45%	15%	30%
U.K. male veterans ³⁴⁹	CMI (modified)	62%	36%	26%
Kansas veterans ²⁸⁵	KS Gulf War Illness	34%	8%	26%
Kansas veterans ²⁸⁵	CMI (modified)	47%	20%	27%
New England Army veterans ²⁴³	CMI (modified)	65%	33%	32%

CMI: chronic multisymptom illness, as defined by Fukuda et al.⁸⁵

As shown in the right column of Table 3, highly consistent estimates of the excess rate of illness in Gulf veterans have emerged from these studies, which used different definitions of “multisymptom illness” in different veteran populations. Regardless of whether the symptom pattern is defined broadly (as in the studies of British and New England veterans) or conservatively (as in the study of Kansas veterans), the excess prevalence of multisymptom illness in Gulf War veterans compared to non-Gulf veterans has consistently been between 26 and 32 percent. The fact that these diverse studies have generated consistent estimates of the excess rate of illness attributable to Gulf War service suggests that this finding is robust, and that between one-fourth and one-third of Gulf veterans have experienced a multisymptom pattern of illness since the war, over and above the “background” level of symptoms expected had this group not served in the Gulf War.

In summary, although many questions remain about the nature and causes of health problems affecting Gulf War veterans, a number of important conclusions can be drawn from existing epidemiologic research. Gulf veterans experience significantly more symptoms, illnesses, and diagnosed conditions than veterans who did not serve in the Gulf War, although these conditions have not generally been associated with increased rates of hospitalization or disease-related deaths. The multisymptom conditions affecting Gulf veterans cannot be explained by wartime stress or psychiatric illness, and affect a substantial proportion of veterans. Population-based studies indicate that between 26 and 32 percent of Gulf veterans experience a multisymptom pattern of illness, over and above the rates experienced by veterans who did not serve in the Gulf War.

Finding 2
Treatments that improve the health of veterans with Gulf War illnesses are urgently needed.

When military personnel become ill or disabled as a consequence of their military service, it is the responsibility of the federal government to address their medical needs. In the years since the Gulf War, Congressional committees, the federal interagency Persian Gulf Veterans Coordinating Board, and expert review panels all have identified adequate treatment for Gulf veterans' illnesses to be a top federal priority.^{136,221,236,304,346,348} The charter of the Research Advisory Committee recognizes that "the fundamental goal of Gulf War-related government research is to ultimately improve the health of ill Gulf War veterans" and directs that "the choice and success of research efforts shall be judged accordingly" (Appendix C). However, in the 13 years since military personnel returned from Desert Storm, little progress has been made in identifying treatments that substantially improve the health of veterans with Gulf War illnesses.

Identifying useful treatments for Gulf War veterans' illnesses is a complex challenge. These conditions are poorly defined, of unknown etiology, and are not generally distinguished by objective clinical markers. The conditions may result from several overlapping causative factors and represent different overlapping pathophysiological processes. It is precisely because of these difficulties and the shortage of promising treatment research from the larger scientific community that VA has a unique responsibility to pursue all scientific and clinical avenues potentially capable of identifying and developing treatments that can improve the health of ill Gulf War veterans.

Successful treatments for medical conditions are generally identified in two ways. The first approach relies on clinical observations over time that certain illnesses respond favorably to certain treatments. Such clinical observations can then be followed by systematic scientific study to evaluate a treatment's effectiveness and determine if it should be recommended for wider use. The second approach involves the rigorous scientific identification of the specific molecular mechanisms underlying a disease, and development of treatments that interfere with the identified disease process. The clinical observation approach may, in some circumstances, be faster and less expensive, but involves trial and error and a mechanism through which clinical experience is converted into systematic scientific information. The molecular mechanism approach requires a determined scientific effort, often involving substantial commitments of time and financial resources. Given the challenges associated with addressing Gulf War veterans' illnesses, it is likely that both approaches will be important for making progress in identifying treatments that significantly improve veterans' health.

The federal government has expended considerable funding on treatment-related research for Gulf War veterans' illnesses. As shown in Table 4, VA and DOD projected spending over 21 million dollars on treatment research for veterans' unexplained illnesses through 2003.⁷³ Over 15 million dollars of this funding was used to conduct two large clinical trials of treatments for Gulf War veterans' illnesses. Additional

funding was allocated for demonstration projects at several VA medical centers. These demonstration projects focused on identifying innovative case management strategies that would improve veterans' quality of life and satisfaction with health care. Although a number of the demonstration clinics did result in improved ratings of patient satisfaction with the enhanced level of services provided, none produced a significant improvement in veterans' overall health status.

Table 4. Federal Research on Treatments for Gulf War Veterans' Illnesses

Project Title	Study Location(s)	Study ID	Program Funding (\$)	Total Allocation (\$)
Antibiotic Treatment of Gulf War Veterans' Illnesses (ABT)	26 VAMCs 2 DOD Hospitals	VA-55 DOD-119	4,150,080 1,500,000	5,650,080
A Randomized, Multi-Center, Controlled Trial of Multi-Modal Therapy in Veterans with Gulf War Illnesses (EBT)	18 VAMCs 2 DOD Hospitals	VA-62 DOD-115	6,560,309 3,000,000	9,560,309
Antibacterial Treatment Method Based Upon the Excretion of Dead and Decaying Spherical Bacteria	Louisiana Medical Foundation	DOD-67	3,400,000	3,400,000
Birmingham's Gulf War Veterans' Illness Demonstration Clinic	Birmingham VAMC	VA-56	476,900	476,900
Case Management and Residential Rehabilitation for Persian Gulf War Veterans	Tampa VAMC	VA-57	500,000	500,000
Demonstration Treatment Program for Gulf War Veterans with Unexplained Physical Symptoms	Cincinnati/Cleveland VAMCs	VA-59	653,475	653,475
Identification and Management of Sleep Disorders in Gulf War Veterans	Boston area VAMCs	VA-60	696,000	696,000
Veterans' Demonstration Project	Portland/Puget Sound VAMCs	VA-58	697,015	697,015
Total Funding				\$21,633,779

Source: *Annual Report to Congress: Federally-Sponsored Research on Gulf War Veterans' Illnesses for 2002*⁷³

VA and DOD jointly funded two large multi-center clinical trials for Gulf War veterans' illnesses: the Antibiotic Treatment Trial (ABT) and the Exercise/Behavioral Therapy Trial (EBT).^{56,75} The ABT was undertaken in response to reports from Dr. Garth Nicolson that some ill Gulf veterans appeared to be infected with mycoplasma, particularly a species previously identified in HIV patients, *mycoplasma fermentans* (incognitus strain).^{186,220} Dr. Nicolson indicated that this chronic infection was intracellular, and so often could not be detected by conventional serological methods.²¹⁹ After working with a number of ill Gulf veterans, he reported that many improved after a prolonged course of antibiotic therapy.²²⁰

The federal ABT trial assessed the efficacy of a 12-month course of the antibiotic doxycycline in improving the health and physical functioning of symptomatic veterans who tested positive for mycoplasma infection. The study included 491 patients at 28 study sites, and is now complete. Study results were summarized in a presentation to the Committee in 2003³⁶³ and have recently been published.⁷⁶ About 40 percent of ill veterans screened for inclusion in the study were found to be positive for mycoplasma species. Study results indicated that about 18 percent of mycoplasma-positive veterans who received doxycycline over a 12 month course of treatment showed improvement, as indicated by an increase of at least seven points in physical function scores assessed using the Medical Outcomes Study Survey Form 36 (SF-36) instrument for veterans.^{170,355} This was nearly identical to the 17 percent of veterans who showed similar improvement after 12 months on a placebo.

The results of this trial thus appear to indicate that doxycycline therapy does not provide significant benefit for Gulf War veterans' illnesses. However, a number of the study findings shared with the Committee were puzzling and raise questions about the study's conclusions. Investigators indicated that laboratory testing for mycoplasma species yielded inconsistent results between the four laboratories initially tasked with testing veterans' blood. As a result, the study design was modified to use testing results provided by just one of the laboratories. The study also found that veterans who received doxycycline therapy did appear to show significantly greater improvement than those taking placebo after three months of therapy. However, differences between the two groups on both primary and secondary measures tapered off over the course of the study, with no significant differences remaining after six months.⁷⁶ After 12 months of treatment, 39 percent of veterans in the doxycycline treatment group had no detectable levels of doxycycline in their blood, indicating that there may have been a significant problem with adherence to the doxycycline regimen. Finally, after 18 months, only about 10 percent of veterans in the study tested positive for mycoplasma, independent of whether they had received doxycycline or placebo. This finding is perplexing in light of the study's initial assessment indicating that 40 percent of all ill veterans tested positive for mycoplasma, and the inclusion of only mycoplasma-positive patients in the study.

The second large government study tested whether exercise and cognitive behavioral therapy, individually or together, would improve the health of ill veterans. Previous research had found these approaches to provide some benefit for chronic fatigue syndrome (CFS) and fibromyalgia patients.^{68,95,238,239,268,359} The EBT study included 1,092 veterans enrolled at 20 study sites. Results were published in March, 2003, and indicated that cognitive behavioral therapy, but not exercise, was associated with improvement in a small but statistically significant proportion of veterans. Specifically, 18.5 percent of veterans who received cognitive behavioral therapy showed at least a seven-point improvement in SF-36 physical function scores. This compared to the 11.5 percent who improved with “usual care”—that is, without receiving either intervention—and the 11.7 percent who improved with exercise alone.⁷⁵ Cognitive behavioral therapy is known to improve function in a number of medical and psychiatric conditions, including clinical depression.^{47,89,111,172,201,267} Additional analyses are needed to determine whether the modest improvements provided by cognitive behavioral therapy in the EBT trial resulted from improvements related to comorbid depression in a subset of ill Gulf War veterans, or, more generally, to improvements in veterans’ medical symptoms.

In addition to research on treatments, VA cooperated with DOD, beginning in 1999, in convening a multidisciplinary panel of clinicians and researchers to develop clinical practice guidelines for the evaluation and management of post-deployment health concerns.³³⁰ The guidelines provide an algorithm for conducting patients’ histories and physical examinations and for laboratory tests to be administered, but do not provide information regarding specific treatments. VA and DOD also convened an expert panel to develop clinical practice guidelines for medically unexplained symptoms, including chronic pain and fatigue.³³¹ These guidelines do provide specific treatment options and recommendations based on published research and the experience and opinions of scientists and clinicians on the panel. Identified treatments are those used by some clinicians to treat CFS and fibromyalgia. Some have not been evaluated in scientific studies for their effectiveness with these conditions, and none have been evaluated for their effectiveness in treating Gulf War illnesses. In addition, no studies or monitoring programs have been established to follow up veterans treated by government physicians who use these guidelines to determine whether the recommended treatments provide benefit to veterans with unexplained multisymptom illnesses.

There has been little effort to date to systematically utilize the combined experience of the many VA clinicians currently treating Gulf veterans in VA medical facilities. No mechanism is currently in place for compiling data on treatments and outcomes documented in the medical records of ill veterans seen by VA clinicians. Research studies of medical outcomes are utilized for other conditions by VA scientists and clinicians,^{170,225,257} but no programs are in place to monitor health outcomes associated with therapeutic approaches used in treating ill Gulf veterans either at local VA medical centers or at VA’s specialty referral clinics for deployment-related

health conditions. And, as previously mentioned, no new programs have been established to evaluate the effectiveness of the therapeutic approaches recommended in VA's clinical practice guidelines for medically unexplained symptoms.

In theory, funding for treatment studies of Gulf veterans' illnesses has long been available to VA researchers interested in pursuing this type of research. VA has maintained an open solicitation for treatment proposals for Gulf veterans' unexplained illnesses since 1997, and further encouraged the submission of treatment proposals in its 2002 program funding announcement for deployment health research. However, with the exception of the two large multi-center trials, VA has funded no studies designed to evaluate the effectiveness of specific treatments for Gulf veterans' unexplained illnesses. The only treatment study currently underway at VA that includes Gulf War veterans is a study comparing two types of psychotherapy for PTSD in women veterans.³³²

VA's usual process for sponsoring treatment studies for Gulf War illnesses and other conditions is, in many respects, passive. That is, the VA Office of Research and Development does not generally direct researchers to conduct specific studies that address specific research questions or evaluate specific treatments. Rather, it requires that VA clinician-researchers with sufficient interest and expertise in treating unexplained illnesses come forward with credible proposals for clinical trials with some level of evidence indicating that the treatment to be studied may be beneficial. There are no VA programs or investigators tasked with identifying innovative treatments for Gulf War illnesses that are potentially beneficial and should receive high priority for study. Nor are there programs or mechanisms in place whereby treatment strategies already utilized by VA or private clinicians can be identified and systematically studied.

Thousands of Gulf veterans are treated for unexplained illnesses every year in VA and DOD clinics and by private physicians. A number of plausible treatment candidates have been suggested by different clinicians as having possible benefit for Gulf War veterans' illnesses, based on case reports, effectiveness in treating similar conditions, and effects on likely mechanisms of illness. But little effort has been made to systematically evaluate these therapies to determine which candidate treatments appear to be suitable for clinical trials, which require further data development, and which appear to hold little potential for benefit. Where there are insufficient data on a potentially promising treatment to warrant moving ahead with large clinical trials, no programs are currently in place to develop such information. Thus, promising treatment candidates perpetually remain only treatment candidates.

Other federal agencies have developed protocols for assessing the effectiveness of treatments used clinically that have not been systematically evaluated or studied. These include the "Best Case Series" approach developed and used at the National Cancer Institute,^{214,356} and the

“Prospective Outcomes Evaluation and Monitoring System” developed at the National Center for Complementary and Alternative Medicine at the National Institutes of Health.²⁵¹ These protocols have been used to make preliminary assessments of the usefulness of unstudied treatments and to provide a framework for making decisions to determine when additional study is warranted.

In 1998, VA asked the Institute of Medicine (IOM) to review existing research relevant to treatments for Gulf War illnesses and similar conditions. Because no treatment research on Gulf War veterans’ illnesses had been completed at that time, the 2001 IOM report and recommendations focused on treatment research methodology and research on conditions with some similarities to Gulf War veterans’ illnesses, including CFS, fibromyalgia, headache, and depression. The IOM report called for a comprehensive approach to treatment guidelines and research on Gulf War veterans’ illnesses that relies on a “hierarchy of evidence,” that is, evidence from a range of study designs that provide different types and strengths of information.¹³⁶

Treatment recommendations for veterans’ illnesses must be based on the best available scientific evidence. Similarly, decisions made regarding the selection of potentially useful treatments for evaluation in large clinical trials should be based on the best available evidence. As described in the 2001 IOM report, a range of study designs is available to researchers that provides different levels of evidence regarding treatment effectiveness, ranging from expert opinion and unsystematic observation, the lowest level of evidence, to multiple well-conducted randomized trials or outcomes studies, the highest level. The report noted that observational designs (including outcomes monitoring studies and well-conducted cohort studies) and small clinical trials can provide important and useful evidence regarding treatment effectiveness. Such studies can often be completed at a fraction of the time and expense of large clinical trials.

In attempting to identify treatments for Gulf War veterans’ illnesses, VA has focused its efforts on the lowest and highest levels of evidence—that is, on the consensus judgment of experts, and on large, multi-center trials. Both have required an enormous amount of effort on the part of government officials, clinicians, and scientists, and have consumed considerable time and financial resources. But unfortunately, neither effort has succeeded in identifying treatments for which there is evidence of substantial health benefits for veterans with unexplained multisymptom conditions.

As indicated, VA generally funds research proposals initiated by researchers in the field, rather than utilizing a “top down” approach that directs specific research questions to be studied using specific protocols. The two large treatment trials of Gulf War veterans’ illnesses were an exception, however, developed in response to an initiative from VA’s Office of Research and Development. The Committee considered this exception to be a positive indication that VA was prepared to take decisive

action in identifying treatments that might benefit ill Gulf War veterans. However, the Committee was concerned that both large clinical trials were undertaken with little systematically generated evidence that the treatments being studied were potentially beneficial for Gulf War veterans. Directives from Congressional committees and government panels that VA identify treatments for Gulf War illnesses likely resulted in considerable political pressure for VA to move forward with these studies. This may explain, in part, why the approaches taken appear to have lacked the level of preliminary development required to optimally study treatments for which investigators had little research or experience on which to rely. In the case of the antibiotic treatment trial, for example, no corroborating evidence was developed prior to the treatment trial to first indicate that the infection in question could be reliably identified and was disproportionately present in ill veterans. Second, if the infection was shown to be present in a substantial number of veterans, it would have been prudent to first conduct one or more studies of smaller size and/or shorter duration to determine whether antibiotic therapy was associated with symptomatic improvement in ill veterans and to optimize a protocol to be used in larger studies. Similarly, smaller studies could also have been used to determine first whether ill veterans appeared to benefit from cognitive behavioral therapy and/or exercise therapy, and to refine the protocols that seemed most capable of producing benefits for ill veterans.¹¹⁸

The results of these studies have been disappointing to ill veterans and to healthcare providers seeking treatments that hold promise for providing substantial benefits for veterans' multisymptom conditions. The Committee concludes that federal efforts have not been successful in identifying effective therapies for Gulf War illnesses, nor in developing a mechanism for identifying and evaluating candidate treatments for assessment in clinical trials. The considerable funding and human resources required to conduct one large multi-center clinical trial might be more productively used to sponsor a range of scientific research activities aimed at identifying, prioritizing, and evaluating treatment options for Gulf War veterans' illnesses. Such activities would include observational research studies, pre-clinical studies, and smaller trials capable of providing crucial preliminary information on the effectiveness of treatments and guidance for optimal application and study of those treatments. Preliminary efforts should include identification of well-defined veteran subgroups for which the treatment under study is most likely to be effective. Such efforts would not preclude the use of large, rigorous clinical trials for evaluating treatments for Gulf War illnesses. Rather, they would establish an evidence-based framework for identifying and prioritizing treatment candidates for clinical trials and enhance the probability that large, expensive trials of useful therapies will be successful.

In light of the difficulties involved and the lack of success to date, it is particularly important that VA take a new and reinvigorated approach to identifying treatments that will benefit ill Gulf War veterans. This

approach must be scientifically rigorous and well-planned and managed, but it must also be bolder and more comprehensive than past efforts.

Finding 2 Recommendations

The Committee recommends that VA immediately establish a comprehensive program specifically tasked with evaluating treatment-related information and research, and developing data and pilot studies as necessary to identify promising candidate treatments for clinical trials for Gulf War veterans' illnesses. This program would employ a multi-faceted approach using and developing evidence from a variety of study types, from case series reports and outcomes research to randomized trials. It should be staffed and managed by professionals with expertise in investigating complex illnesses and in evidence-based methodological approaches to treatment development and evaluation. This initiative would include support for pilot studies of potentially promising treatments for Gulf War veterans' illnesses and would augment VA's current strategy of supporting clinical trials of scientific merit as they are proposed by VA scientists in the field.

The recommended program would include the following components:

- Identification of treatments used by clinicians and veterans for Gulf War veterans' illnesses. Current and previously used treatments can be identified in a variety of ways, including compilation of existing clinical data on treatments administered by VA clinicians and systematic surveys of veterans and clinicians regarding treatments.
- Collection of retrospective and prospective observational data on clinical outcomes associated with treatments used by clinicians, particularly treatments used in VA specialty clinics for Gulf War veterans, and those recommended for use by VA clinical practice guidelines for medically unexplained fatigue and pain.
- Development of a plan for developing and testing innovative but untried treatment strategies. Priority among treatments to be developed and tested should be determined by such considerations as plausibility of benefit based on likely pathophysiological mechanisms of illness, proven effectiveness in treating symptoms or symptom complexes similar to those experienced by Gulf War veterans, and potential for adverse side effects. This plan should include cooperative research with scientists and clinicians outside the VA system with expertise in testing or administering innovative therapies not currently available at VA.
- Development of a general protocol for assessing the evidence on the potential benefit of treatments for Gulf War veterans' illnesses in order to determine which ones appear to be suitable for clinical trials, which require further data development and evaluation, and which appear to hold little potential for benefit.

Finding 2

- Provision of technical assistance and research support to clinicians—both those who currently treat Gulf War veterans' illnesses and those with expertise in administering treatments that may hold promise for these conditions—in developing evidence regarding the effectiveness of treatments.
- Development of guidelines for standardizing essential parameters of Gulf War illness treatment research, including documentation of the definition and measures used to define multisymptom illness and illness subgroups, documentation of the treatment intervention, and measurement of health status before and after the treatment intervention.

Finding 3
A growing body of research indicates that an important component of Gulf War veterans' illnesses is neurological in character.

Gulf War veterans have reported symptoms suggestive of neurological dysfunction since their return from Desert Storm in 1991.^{69,150,303} However, without specific information about the types and concentrations of exposures experienced by individual veterans, consideration of a link between Gulf War service and neurological pathology must rely on two types of evidence. First, it must be determined whether Gulf War veterans, in fact, do exhibit excess neurological pathology or functional impairment relative to comparison groups. Several different lines of research have addressed questions regarding neurological impairment in Gulf veterans, and are summarized below. Second, it is important to consider evidence concerning the potential for events or exposures associated with service in the Persian Gulf theater to have caused chronic neurological sequelae, as summarized in Finding 4 of this report. After reviewing research and testimony relating both to neurological impairment in Gulf War veterans and to neurotoxic exposures in theater, the Committee concludes that a growing body of evidence indicates that an important component of Gulf War veterans' illnesses is neurological in character.

Increased risk of amyotrophic lateral sclerosis in Gulf War veterans. The most sobering indication of neurological disease in Gulf veterans comes from two studies released in 2003 which determined that Gulf veterans have developed amyotrophic lateral sclerosis, commonly referred to as ALS or Lou Gehrig's disease, at about twice the rate of comparison populations in the years since Desert Storm.^{103,117} ALS is a progressive neurodegenerative disease, with less than 10 percent of patients surviving more than five years after initial diagnosis.^{70,277}

One of the two studies investigating the rate of ALS in Gulf veterans indicated that the excess risk among deployed veterans may be of particular concern among younger veterans—that is, those under age 45, who are generally least likely to develop this disease.¹⁰³ The study found that the rate of ALS among younger veterans was similar to that of the general population in the first four years after the war, but increased progressively from 1995 through 1998, the last year in which data were assessed. Two-thirds of the young veterans with ALS in this study were reported to have returned from the war with chronic symptoms typical of Gulf War veterans' illnesses, but developed serious progressive ALS symptoms between five and eight years later.

It is of great concern that the full impact of this disease on Gulf War veterans might not be known for decades. In the general population, the majority of ALS cases are first diagnosed after age 55.^{21,202,277} By the end of the year 2000, the most recent year included in VA's ALS study, fewer than three percent of Gulf veterans had reached age 55. As shown in Table 5, data from that study indicate that the rate of ALS in Gulf veterans exceeded that in nondeployed veterans in all age groups.²²⁶ Estimates from this study are based on small numbers, and so must be interpreted with caution. But it is important that this condition be monitored in Gulf War veterans for many years to come, since it is possible that the excess number of ALS cases may continue to rise as veterans age. To address this

concern, VA now maintains a registry for veterans of all eras who have been diagnosed with ALS. VA also provides service-connected disability compensation for Gulf War veterans diagnosed with ALS on a case-by-case basis, although no regulation granting presumed service-connection for all Gulf War veterans with ALS has been established.

Table 5. Age-Specific ALS Rates in Gulf Veterans, Nondeployed Veterans, and a Comparison Population
(number of ALS cases per 100,000 population)

Age at ALS Onset	Gulf War Veterans ²²⁶ (40 ALS cases)	Nondeployed Veterans ²²⁶ (67 ALS cases)	Men in the state of Washington ²⁰² (127 ALS cases)
< 25	0.08	0.00	0.11
25-34	0.45	0.26	0.79
35-44	1.77	0.80	1.63
45-54	5.64	4.81	2.49
55-64	31.19	8.89	6.42

Neurological symptoms in Gulf War veterans. With the exception of ALS, research studies have not comprehensively assessed rates of diagnosed neurological diseases in Gulf War veterans. But symptoms suggestive of neurological problems have consistently been among those most commonly reported by ill veterans. Such symptoms include chronic headaches, memory problems, difficulty concentrating, sleep disturbances, problems with balance, numbness and tingling in extremities, and mood changes.

A number of epidemiologic studies have grouped the many unexplained symptoms reported by Gulf veterans into categories using statistical techniques. Although specific details vary with the types of symptoms queried and the statistical methods used, symptom groups suggestive of neurological, neurocognitive, and/or neuropsychological dysfunction are consistently identified in population-based studies of Gulf War veterans, as summarized in Table 6.

Identified neurological symptom complexes generally occur in both Gulf-deployed and nondeployed veteran groups, but always at significantly higher rates in Gulf War veterans. However, in VA's national survey of over 20,000 veterans, a unique neurological symptom factor was identified only in Gulf War veterans, not in nondeployed Gulf War era veterans. This cluster of symptoms included blurred vision, loss of balance/dizziness, tremors/shaking, and speech difficulty. Gulf War veterans with this

symptom complex also had significantly elevated rates of seizures, migraine headaches, and neuralgias compared to veterans who did not have these symptoms.¹⁵⁹

Table 6. Neurological Symptom Groups/Factors Identified in Gulf Veteran Populations

Population	Identified Symptom Group	Representative Symptoms
Navy construction battalion ¹⁰⁸	Impaired cognition	Attention problems, short-term memory problems, depression, daytime somnolence, slurred speech
	Confusion-ataxia	Reasoning problems, confusion, vertigo, memory problems
Pennsylvania Air National Guard ⁸⁵	Mood/cognition	Difficulty concentrating or remembering, trouble finding words, difficulty sleeping, feeling depressed
U.K. veterans ⁵¹	Peripheral	Tingling in hands or feet, loss of sensation in hands and feet, cramps or spasms in muscles, itching skin
	Neurological	Loss of balance, double vision, feeling dizzy, feeling weak, unsteady when walking
Kansas veterans ²⁸⁵	Neuro/cognitive/mood	Headaches, short term memory problems, blurred vision, dizziness, sensitivity to light, feeling depressed
U.K. male veterans ¹⁴⁰	Mood/cognition	Headaches, irritability, sleeping difficulties, fatigue, forgetfulness, loss of concentration
	Peripheral nervous system	Tingling in legs or arms, numbness or tingling in fingers or toes
Nationwide sample of U.S. veterans ¹⁵⁹	Fatigue/depression	Concentration and memory problems, excess fatigue, feeling depressed, sleep difficulties
	Neurological	Blurred vision, dizziness, speech difficulty, tremors/shaking

As shown in Table 6, symptoms suggestive of neurological problems have consistently been reported by ill veterans and characterized in research studies. Routine physical examinations and diagnostic tests have generally not provided explanations for the nature and causes of these symptoms.^{37,85,106,108} However, more specialized assessments of Gulf War veterans conducted in research settings have begun to provide objective evidence of neurological abnormalities in symptomatic Gulf War veterans.

Objective evidence of neurological impairment in Gulf War veterans. A growing number of studies, from different research groups studying different Gulf War veteran populations, have identified neurological abnormalities in ill Gulf War veterans using objective testing methods. Associations between veterans' unexplained symptoms and neurological pathology have been demonstrated using specialized neuroimaging techniques, tests of autonomic nervous system function, audiovestibular testing, and measures of neuropsychological function in Gulf veterans relative to comparison groups.

Neuroimaging and neurohormonal studies. In a 1997 case-control study, researchers at the University of Texas Southwestern Medical Center found no evidence of structural differences between the brains of ill veterans and controls on standard magnetic resonance imaging scans (MRI).¹⁰⁶ But because of similarities between Gulf veterans' symptoms and early symptoms of diseases of the basal ganglia such as Huntington's, Wilson's, and Fahr's diseases,¹⁸³ these investigators conducted more specialized neuroimaging studies to assess deep brain structures in ill Gulf War veterans. Using long echo time proton (¹H) magnetic resonance spectroscopy (MRS), they assessed brain cell health in the brainstem and right and left basal ganglia of 22 ill Gulf veterans and 18 matched veteran controls.¹⁰⁹ Results indicated that the ratio of N-acetyl-aspartate to creatine (NAA/Cr), a measure of functional brain cell mass, was significantly lower in all three brain regions of ill Gulf veterans than in controls. Also importantly, the specific regions of the brain affected differed between veterans with different symptom profiles. In the most severely disabled veterans (those defined as having Haley Syndrome 2), the NAA/Cr ratio was reduced in all three brain regions. Veterans with other defined symptom profiles (Haley Syndromes 1 and 3) showed reduced functional brain cell mass in either the brainstem or the basal ganglia, but not in both. This team was able to replicate these findings in a separate group of six Army veterans with Syndrome 2, who were also found to have reduced NAA/Cr ratios in all three brain regions.¹⁰⁹ Researchers concluded that Gulf War veterans with different clinical syndromes have biochemical evidence of different anatomical distributions of brain cell damage as demonstrated by proton magnetic resonance spectroscopy.

Following these reports, scientists at the San Francisco VA Medical Center and the University of California at San Francisco undertook an independent study to test these findings. In an initial study comparing 11 ill Gulf veterans whose symptoms met the definition of Haley's Syndrome 2 to 11 non-veteran controls, investigators performed a similar protocol of long echo time proton MRS on the right basal ganglia, with additional methodological refinements. Results showed a reduction in the NAA/Cr ratio similar to that observed in the Texas study.²⁰⁵ These researchers are currently conducting studies to further investigate these neurological abnormalities in a larger sample of ill veterans.

In conjunction with the Texas MRS studies, Haley and colleagues assessed the level of central dopamine activity in the basal ganglia of ill

veterans and controls. Dopamine is a neurotransmitter in the brain that plays a critical role in the control of movement. In the study, after veterans spent six days in a low-stress clinical environment consuming a low tyrosine diet, fasting venous blood samples were drawn to assess the levels of two chemicals (homovanillic acid and 3-methoxy-4-hydroxyphenylglycol) whose ratio provides an index of dopamine production in the central nervous system. Veterans who had exhibited more brain cell damage in the left basal ganglia (lower NAA/Cr ratio) had significantly higher brain dopamine production. This association was not found in the right basal ganglia, suggesting that dopaminergic pathways in the basal ganglia may have been damaged in a lateralized pattern. Investigators concluded that these results support the view that Gulf War illnesses are associated with neurological damage, in part resulting from injury to dopaminergic neurons in the basal ganglia.¹⁰⁵

An additional neuroimaging study of interest comes from investigators affiliated with the Montgomery VA Medical Center in Jackson, Mississippi, who used MRS to evaluate the hippocampus region of the brain in a small sample of ill Gulf War veterans.²⁰⁴ The hippocampus is a highly vascularized inner brain region involved in a variety of functions, including those associated with spatial orientation, memory, and mood. The study found that symptomatic Gulf veterans had significantly reduced NAA/Cr ratios in both the right and left hippocampus areas, in comparison to healthy controls. While preliminary, such findings raise the concern that ill Gulf War veterans may have neuronal damage in multiple regions of the brain.

Autonomic nervous system dysfunction. The autonomic nervous system is the portion of the nervous system that controls the many physiological processes that are virtually “automatic”—that is, not generally under our conscious control. These include such diverse processes as regulation of heartbeat and blood pressure, response to stressful stimuli, digestion of food, sexual function, and regulation of body temperature. One of the first scientific studies suggesting possible autonomic dysregulation among Gulf War veterans was presented at a 1998 federal research conference. Investigators provided preliminary data indicating that Gulf War veterans had an excess rate of gall bladder disease requiring cholecystectomy compared to other veterans, and suggested this could have been the result of bile stasis due to autonomic dysfunction.²⁰⁶

Function of the autonomic nervous system can be assessed by monitoring heart rate and blood pressure in response to different challenges. One commonly used approach involves tilt table testing, in which blood pressure, heart rate, and symptoms are monitored both in a supine position and when subjects are tilted to an upright position. Abnormalities on this test have been demonstrated in a number of conditions affecting the autonomic nervous system, including chronic fatigue syndrome.^{36,83,91} Investigators from Evans Army Hospital in Colorado have reported that symptomatic Gulf veterans were significantly more likely to have abnormal adaptive responses to tilt table testing than

healthy controls.⁶⁷ Researchers from the East Orange, New Jersey, VA Medical Center also found that ill Gulf War veterans have blunted cardiovascular responses to stressors compared to healthy veterans.²³¹ In addition, Haley and colleagues have reported that high frequency heart rate variability was significantly blunted during sleep in ill Gulf veterans compared to healthy veterans, another indication of autonomic dysfunction in symptomatic veterans.¹¹⁰

Early findings of abnormal autonomic regulation in ill Gulf War veterans have been supported and expanded by a larger and more comprehensive study of autonomic function in Gulf War veterans sponsored by the Department of Defense and conducted by investigators at Midwest Research Institute.²⁵⁸ Portions of this project are still underway and autonomic testing results have not yet been published. In a presentation to the Committee, Dr. Antonio Sastre reported that ill Gulf veterans significantly differed from controls on a wide range of autonomic tests and measures, including heart rate and blood pressure responses to tilt table testing. In these tests, autonomic responses were generally blunted in symptomatic Gulf veterans relative to controls. Investigators also noted that, consistent with an earlier study,²⁶⁶ ill veterans did not exhibit abnormalities when tested using the Valsalva maneuver, suggesting that this single measure does not adequately characterize autonomic function in symptomatic Gulf veterans. If supported by scientific peer review, the results of this study will provide a strong indication of autonomic dysfunction in symptomatic Gulf War veterans, as evidenced by a consistent pattern of differences between ill veterans and controls on a broad range of autonomic measures.

Additional neurophysiological assessment of ill Gulf veterans.

Dizziness and problems with balance are frequently reported by symptomatic Gulf War veterans. In 1997 and 2000, University of Texas Southwestern investigators reported results of audiovestibular assessments of ill veterans undertaken to determine whether these symptoms are neurological or functional in nature.^{106,255} Audiovestibular tests assess the function of auditory pathways from the inner ear through the brainstem. Specific identified abnormalities can sometimes be used to determine the location of pathology in these pathways. Overall, researchers found that symptomatic veterans were significantly more likely to exhibit abnormal ocular motility, pathologic eye movements (nystagmus), and asymmetric eye reflexes than matched controls, with specific abnormalities differing between veterans meeting criteria for Haley's three defined syndromes. Investigators concluded that veterans' reports of balance difficulties are due to a true vertigo that is organic in nature, resulting from a subtle abnormality of central vestibular function mediated by neural pathways in the brainstem or basal ganglia.

Studies of peripheral nerve function in Gulf War veterans have produced mixed findings. In 1996, a British study reported the results of neurophysiological testing of 14 symptomatic Gulf War veterans and 13 healthy civilian controls.¹⁴⁴ Investigators found significant differences

between the groups on three measures related to peripheral nerve function. Most prominent was a finding that the threshold for detecting subtle changes in cold temperatures was significantly higher in Gulf War veterans than controls, an indication of impaired function of peripheral small nerve fibers or central sensory processing. In 2000, researchers from the East Orange, New Jersey, VA Medical Center reported that quantitative sensory testing revealed elevated tactile thresholds in symptomatic Gulf veterans compared to controls, but no differences in heat pain perception.^{231,232} In contrast, a British study that year found no evidence of impaired temperature threshold or other sensory measures in symptomatic Gulf veterans compared to comparison groups.²⁶⁶

Neuropsychological testing in Gulf War veterans. Neuro-psychological tests measure brain function by assessing skills associated with cognitive tasks such as memory, attention, problem-solving, and visual-spatial analysis. Such tests are sensitive to the effects of many types of brain injury and disease, including more subtle effects of damage due to some neurotoxic exposures.^{15,80} Patterns of poor performance on specific tests can sometimes be used to identify the location of damaged neurological structures or pathways, providing useful information regarding patients' functional and rehabilitation needs.

Ill Gulf War veterans have regularly reported cognitive symptoms such as problems with short-term memory and difficulty thinking or concentrating. Some researchers have speculated that the excess risk of accidents among Gulf War veterans may be the result of unrecognized or untreated attention and cognitive problems.^{29,102} Numerous studies have evaluated the extent to which veterans' self-reported cognitive symptoms are associated with objective measures of impaired neuropsychological function. Overall, these studies have found ill Gulf War veterans to exhibit deficits on a variety of neuropsychological measures of cognitive performance, in comparison to control groups or population norms.^{16,25,43,62,92,106,116,185,207,272,291,294,358} One team of investigators found that symptomatic Gulf veterans performed worse on global tests of neurocognitive function and intelligence than non-symptomatic controls,¹¹⁶ but the majority of studies have reported that ill Gulf War veterans exhibit impairment in more limited domains of neuropsychological performance. Overall, studies have found that psychological factors are often associated with impaired neuropsychological performance, but do not account for the full range of cognitive deficits observed in ill veterans.³⁵⁷

In 1999, researchers at the Portland VA Medical Center screened a sample of ill Gulf War veterans and found them to have slowed neurobehavioral performance relative to healthy controls.¹⁶ For the most part, these abnormalities were limited to a subgroup of about 20 percent of the symptomatic veterans, distinguished by their poor performance on objective tests of memory, attention, and response speed. Larger follow up studies confirmed that, overall, ill Gulf War veterans performed significantly worse than controls on these tests,²⁹⁰ and again identified a bimodal distribution of neurocognitive impairment in ill Gulf veterans,²⁹¹

indicating that objective indicators of cognitive dysfunction are disproportionately found in a subgroup that is distinct from other symptomatic Gulf War veterans. Investigators pointed out that this subgroup of ill veterans exhibit a pattern of neurobehavioral performance deficits consistent with those observed in organophosphate-poisoned workers, and suggested that research in this area focus on this subgroup, rather than on all symptomatic Gulf War veterans.

More recently, a 2003 study conducted at the Boston VA Environmental Hazards Research Center compared the performance of 207 treatment-seeking Gulf War veterans to 53 non-Gulf veteran controls on a battery of neuropsychological tests. Gulf War veterans scored significantly worse than nondeployed era veterans on measures of attention, visual-spatial skills, verbal memory, visual memory, and mood. Performance scores of Gulf veterans diagnosed with PTSD were similar to scores of veterans who did not have this condition. However, Gulf War veterans who reported taking pyridostigmine bromide (PB) during the war scored significantly worse on a number of neurocognitive measures than Gulf veterans who had not used PB.²⁹⁴

In summary, multiple studies have documented similar complexes of neurological symptoms among different groups of ill Gulf War veterans, as well as objectively-identified neurological abnormalities. Gulf War veterans have significantly elevated rates of the progressive neurodegenerative disease ALS. In addition, neuroimaging studies, tests of autonomic function, and neuropsychological testing have independently identified significant differences between symptomatic Gulf veterans and healthy comparison groups. Although much additional work remains in replicating and expanding these findings, taken together, this body of research provides compelling evidence that an important component of the unexplained illnesses experienced by Gulf War veterans is neurological in character.

Finding 3 Recommendations

The Committee recommends that VA expand research efforts that investigate and characterize possible neurological abnormalities in ill Gulf War veterans. Specifically, VA should:

- Enlist the expertise of specialists in the neurosciences to develop a comprehensive research initiative capable of examining both neurophysiological and neuropsychological function in symptomatic Gulf War veterans in comparison to healthy controls. This effort should emphasize research protocols capable of identifying specific pathways associated with neurological pathology and include comparisons between subgroups of ill Gulf War veterans characterized by their individual symptom profiles and exposures encountered in theater. Protocols should include evaluation of neurological function under dynamic as well as static conditions.

- Expand research efforts that utilize state-of-the-art neuroimaging technology to better characterize differences between ill Gulf War veterans and comparison groups. This should include studies that follow up and extend previously published findings in Gulf War veterans and other chemically exposed populations using magnetic resonance spectroscopy as well as other imaging techniques suited to study brain cell injury and dysfunction, such as functional magnetic resonance imaging (fMRI), positron-emission tomography (PET), single photon emission tomography (SPECT), 128-channel electroencephalography (EEG), and magnetoencephalography (MEG).
- Develop a comprehensive research strategy designed to evaluate and expand on the growing body of evidence regarding autonomic dysfunction in ill Gulf War veterans. This effort should give priority to protocols capable of determining which specific aspects of the autonomic regulatory system are affected in symptomatic veterans. As with other studies involving neurological pathology, studies should investigate autonomic function in defined veteran subsets, grouped according to symptom types and exposures encountered during the war.
- Establish a brain bank to collect and maintain samples of autopsy materials from Gulf War veterans for study.

Finding 4
Evidence supports a probable link between exposure to neurotoxins and the development of Gulf War veterans' illnesses.

Recent findings demonstrating neurological pathology and impairment in Gulf War veterans necessitate a consideration of the possible causes of those problems in conjunction with the many symptoms reported by ill veterans. It has long been known that at least 100,000 troops were potentially exposed to low levels of nerve agents in one incident involving demolition of a weapons storage site in the days just after the Gulf War cease-fire. A recent government report suggests that the number of troops potentially exposed as a result of this and other incidents may have been even greater. This information is of particular concern in light of recent animal studies indicating that, contrary to previous assumptions, exposure to low levels of nerve agents can produce chronic neurological and immunological effects, even in the absence of obvious immediate symptoms of exposure.

Epidemiologic studies of Gulf War veterans have linked a number of exposures of potential concern in the Persian Gulf theater to higher rates of symptoms and illnesses. Among the most prominent risk factors consistently identified are substances that can adversely affect the nervous system. Chemical nerve agents, pyridostigmine bromide, and some types of pesticides all have similar modes of action; they work by inhibiting a specific enzyme involved in the metabolism of the neurotransmitter acetylcholine. After reviewing a large body of evidence concerning exposure to these types of compounds in theater, their potential effects alone and in combination, and their associations with illness in studies of Gulf War veterans and other populations, the Committee concludes that evidence supports a probable link between exposure to neurotoxins during the Gulf War, most prominently acetylcholinesterase inhibitors, and the development of Gulf War veterans' illnesses.

Neurotoxic exposures during the Gulf War. The question of whether Gulf War veterans were exposed to chemical weapons has long been debated. Prior to the war, military officials were greatly concerned that the Iraqi regime would use chemical agents offensively during the war, as they had in their recent war with Iran.¹¹⁴ Thousands of chemical alarms were reported to have sounded during the war, and when veterans began to report unexplained symptoms after they returned home many believed that these conditions were the result of chemical exposures. Early government reports maintained, however, that there had been no confirmed offensive use of chemical weapons during the war, requiring a consideration of other explanations. Anecdotal reports from veterans indicated that some had become ill when they took NAPP pills, the nerve agent prophylaxis pill with the active ingredient pyridostigmine bromide (PB), taken as a protective measure in the event of chemical attack. Others voiced concerns about the heavy use of multiple types of insect repellants and pesticides during deployment, due to the profusion of insects and the risk of infectious diseases in the desert environment. Excess pesticide exposure has been associated with chronic neurological symptoms in humans, and animal research has indicated that some combinations of pesticides, or pesticides in combination with PB and/or nerve agents, can produce greater damage

than exposure to any of these compounds alone. Therefore a number of neurotoxins encountered during the Gulf War must be considered for their possible contribution to the chronic illnesses and unexplained symptoms affecting veterans. For each category of exposure, it is important to evaluate evidence relating both to the extent of exposure and the potential for such exposures to cause chronic illnesses similar to those experienced by veterans.

Exposure to chemical weapons during the Gulf War.

19 Jan 91. Seabees of Naval Mobile Construction Battalion 24, stationed near the port of Al Jubayl, report a bright flash in the night sky followed by a detonation-concussion. Chemical alarms sound, and troops don MOPP gear. After the all clear, troops unmask and experience an acrid smell, choking, profuse nasal secretions, facial numbness, a burning sensation on exposed skin and a metallic taste in the mouth. Two M256 detection kits are positive for chemical blister agent. During the weeks following the incident, many of the exposed troops develop skin rashes and chronic ailments.

- Evidence Iraq Used Chemical Weapons
During the 1991 Persian Gulf War³⁰⁰

In the early years following the Gulf War, government reports indicated that it was unlikely that exposure to chemical agents during the war could have contributed to veterans' unexplained health problems, since there had been no documented use of chemical weapons in theater. Conclusions regarding chemical weapons exposures were called into question when, in 1996, reports emerged verifying that chemical agents had been present in theater and that U.S. military personnel had been in the area of a large weapons storage depot containing nerve agents near Khamisayah, Iraq, when it was destroyed after the ceasefire. Verification of this incident brought about a dramatic change in thinking about chemical weapons exposures during the war. The Department of Defense reported that the weapons depot had contained the nerve agents sarin and cyclosarin, and sponsored multiple efforts to estimate how many and which veterans may have been exposed and at what levels. Investigators concluded, after several intensive modeling efforts, that approximately 100,000 U.S. troops may have been exposed to low levels of nerve agents as a result of the Khamisayah demolitions.³²⁰

While the estimate of 100,000 troops is disturbing, it is still unclear whether or not it represents a good approximation of the total number of personnel who may have been exposed to nerve agents during the Gulf War. Contrary to regulations, military logs detailing nuclear, biological, and chemical weapons incidents during Desert Shield and Desert Storm were destroyed after the war.³⁰⁶ Reports from government and non-government sources have described multiple incidents involving evidence of possible chemical weapons exposures in addition to the Khamisayah incident.^{79,300,307-310,312-319,337,347} Military reports indicate that 75 percent of

chemical targets, including weapons manufacturing and storage sites, were destroyed during the war.⁶⁶ A recent report from the U.S. General Accounting Office (GAO, renamed the Government Accountability Office in July, 2004) found that DOD's Khamisiyah modeling efforts were seriously flawed and that available evidence indicates there were likely to have been multiple additional incidents during the war that potentially exposed Coalition troops to chemical weapons.³⁴³ As a result, GAO investigators concluded that the total number of Gulf War veterans who may have encountered low-level exposures to nerve agents in theater may exceed that currently identified in association with DOD's Khamisiyah plume models.³⁴⁵ The GAO report also concluded that results of epidemiologic studies that have relied on DOD's plume models to evaluate health effects related to the Khamisiyah exposures are likely to be unreliable.

Does low-level exposure to chemical agents cause chronic illness? Letters sent by DOD advising Gulf War veterans that they might have been exposed to low-level nerve agents in association with Khamisiyah also indicated that there was little concern that such exposures would lead to adverse health consequences. Conventional wisdom had long held that low-dose exposure to nerve agents—that is, levels that do not cause acute signs and symptoms at the time of exposure—are not expected to cause delayed or chronic health problems. Until recent years, however, it appears that relatively little research had been done that specifically addressed this issue. Assumptions regarding low-dose exposures may have been based, to some extent, on early observations that individuals who became temporarily ill after exposure to less-than-lethal doses of nerve agents appeared, in general, to fully recover.²⁸⁹ It is unclear whether systematic evaluations were done in connection with wartime or accidental human exposure to nerve agents in order to determine if those affected experienced symptoms of ill health that were not immediately apparent or symptoms that persisted over an extended time period following exposure. A 1982 report from the National Academy of Sciences concluded that “although no evidence has been developed to date that any of the anticholinesterase test compounds surveyed carries long-term adverse human health effects in the doses used, the panel is unable to rule out the possibility that some anti-ChE agents produced long-term adverse health effects in some individuals.”²¹³

An interesting report describes a “cerebro-organic delayed effect syndrome” affecting Germans in the 1950s who had worked as chemical weapons production and storage workers in the 1930s and 1940s in facilities that manufactured a variety of chemical agents, including sarin.^{282,283} Years after their employment, these workers reported experiencing persistent nonspecific symptoms (for example, fatigue, headache, gastrointestinal problems, chemical intolerances, memory deficits) as described in the following excerpt.

A neuropsychiatric delayed-effect syndrome was found as a result of systematic investigations of former members of chemical weapons production and testing stations for the Wehrmacht. In terms of frequency, two groups of symptoms can be distinguished—each consisting of separate symptoms or signs.

1. The great majority of persons examined show:
 - persistently lowered vitality accompanied by marked diminution in drive
 - defective autonomic regulation leading to cephalgia, gastrointestinal and cardiovascular symptoms, and premature decline in libido and potency
 - intolerance symptoms (alcohol, nicotine, medicines)
 - impression of premature aging
2. Further, one or more symptoms of the second group were found:
 - depressive or subdepressive disorder of vital functions
 - cerebral vegetative (syncopal) attacks
 - slight or moderate amnesic and demential defects
 - slight organoneurological defects

...On the basis of our studies of the etiologically different manifestations of intoxication, the possibility of a relatively uniform—though equally unspecific—cerebro-organic delayed effect syndrome is conceivable.

- U. Spiegelberg, from a report on a group of German World War II chemical weapons workers who had filed a lawsuit in conjunction with their chronic ill health.^{282,289}

Although the exact types and combinations of exposures is not known for these German workers, this early report does provide an indication that the development of a delayed and chronic syndrome following low level exposure to chemical agents is, in the words of the investigator, “conceivable.”

Sarin exposures in Japanese terrorist incidents. World events since the end of the Gulf War have mandated a closer look at the question of possible chronic effects resulting from low-dose exposure to nerve agents. Human experimental studies of nerve agent exposure are no longer conducted, of course, but observational studies of individuals exposed to sarin in two Japanese terrorist incidents in the 1990s have provided useful insights. In 1994, a terrorist incident in Matsumoto City, Japan, resulted in the exposure of over 600 individuals to sarin and seven deaths.^{208,227} The next year, over 5,000 people were exposed to sarin in a subway terrorist attack in Tokyo that resulted in 11 deaths. Many victims exhibited acute signs of toxicity following these incidents, including miosis (pupil constriction), seizures, tachycardia, respiratory distress, headache and nausea.^{208,228,295} Follow-up investigations have been conducted on survivors of both incidents, although no follow-up studies of individuals who

reported no symptoms at the time of exposure have been reported.^{210,212} Studies have indicated that overt clinical signs of exposure generally resolved within 30 days.²⁰⁸ However, more than six months after the attacks, less overt, chronic abnormalities were observed in electroencephalography (EEG) measures of evoked potentials²¹⁰ and postural sway measures of vestibulo-cerebellar function.^{366,369} The most extended follow up involving a large number of victims reported thus far found that, approximately three years after the Matsumoto attack, about one fourth of those exposed continued to experience a variety of symptoms, including weakness, fatigue, blurred vision, and sleep disturbances.²¹¹

Posttraumatic stress disorder also occurred among some victims of the Japanese terrorist attacks, requiring researchers to assess possible chronic effects of sarin exposure in the context of psychiatric symptoms resulting from traumatic stress. Investigators have generally concluded that psychiatric symptoms exhibited by survivors may be the result of the trauma of the experience, while other symptoms and neurobehavioral deficits are likely attributable to the long term effects of sarin exposure.^{210,223,298,367,368}

Animal studies of chronic effects of low-level sarin exposure.

Scientific understanding of the potential for low-level nerve agent exposures to produce chronic adverse health consequences has been dramatically advanced by a large number of animal studies published in rapid succession in recent years. These studies were sponsored, for the most part, by the U.S. Department of Defense and by the Purkeyne Military Medical Academy in the Czech Republic. Key findings from studies assessing chronic health effects of low-dose sarin exposure are summarized in Table 7. As shown, these studies investigated a variety of parameters measured after variable latency periods following sarin exposure at doses too low to produce immediate signs of toxicity.

These animal studies indicate, in general, that low-dose sarin exposure is associated with chronic indicators of both neurological and immunological impairment. A group of interrelated studies of particular interest comes from Lovelace Respiratory Research Institute in New Mexico. These studies, sponsored by DOD, were published together in 2002. The first study reported that 30 days after rats were exposed to low-dose levels of inhaled sarin—that is, levels that did not induce immediate observable reactions—acetylcholinesterase levels and muscarinic 1 (M1) receptors were reduced, while muscarinic 3 (M3) receptors were increased in particular regions of the brain associated with memory and cognitive function (frontal cortex, basal ganglia, hippocampus, and olfactory bulb).¹¹³ A second study found no effect of low-level sarin exposure on rats' body temperature or locomotor activity.⁵⁷ However, the third study reported significant immunosuppressive effects of subclinical sarin exposure, as indicated by reductions in antibody formation and T-cell proliferation in response to mitogens and antigens. Investigators also determined that these effects appeared to be mediated by the autonomic nervous system, since immune suppression did not occur when an autonomic blocking agent was

administered to sarin-exposed rats.¹⁵¹ Also intriguing was a finding that low-level sarin exposure produced significantly reduced levels of corticosterone, an adrenal hormone generated in response to stressors.^{151,182}

Table 7. Studies of Chronic Effects of Low-Dose Sarin Exposure in Animals

Study	Year	Animal Model	Major Finding
Burchfiel ⁴⁴	1976	monkey	Persistent effects on electroencephalograph readings
Husain ¹²⁸	1993	mouse	Delayed development of spinal cord lesions
Jones ¹⁴⁹	2000	rat	Chronic reduction in nicotinic ACh receptor binding in cerebral cortex
Kassa ¹⁶⁵	2000	rat	Chronic alteration in immune function (lymphocyte proliferation, bactericidal activity of macrophages)
Kassa ¹⁶⁷	2000	rat	Persistent changes in DNA and protein metabolism in liver tissues
Kassa ¹⁶⁶	2001	rat	Subtle chronic signs of neurotoxicity and immunotoxicity with repeated exposures
Kassa ¹⁶¹	2001	rat	Impaired spatial memory
Conn ⁵⁷	2002	rat	No persistent effects on reported indices of temperature regulation and motor activity
Henderson ¹¹³	2002	rat	Delayed, persistent changes in cholinergic receptors in brain areas associated with memory loss and cognitive changes
Hulet ¹²⁶	2002	guinea pig	Persistent failure to habituate on functional test battery
Scremin ²⁶³	2002	rat	Persistent increase in cerebral blood flow in specific areas
Kalra ¹⁵¹	2002	rat	Suppression of immune response (antibody-forming cells and T cell responses) mediated by the autonomic nervous system
Roberson ²⁵⁴	2002	guinea pig	Chronic depression of AChE activity, persistent behavioral changes (disordered activity, increased rearing behavior)
Husain ¹²⁷	2003	mouse	Persistent reductions in respiratory exchange, blood AChE activity and BChE activity, NTE activity in various tissues
Scremin ²⁶²	2003	rat	Down-regulation of muscarinic receptors in hippocampus, decreased habituation
Kassa ¹⁶²⁻¹⁶⁴	2003 2004 2004	mouse	Chronic alteration in immune function (increase in CD19 cells, decrease in CD4 cells, decrease in mitogen-induced lymphoproliferation, increased NK cell activity)

Other research groups have also reported evidence of altered immune function, as well as physiological and behavioral indicators of neurological changes that result from low-level sarin exposure, as shown in Table 7. In addition, the Committee will follow with interest preliminary reports presented at the March, 2004, conference of the Society of Toxicology, from studies suggesting that low-dose sarin exposures may initiate persistent changes in the expression of genes involved in processes relevant to brain cell injury and inflammation.^{87,264}

Given the probability that a significant number of Gulf War veterans may have been exposed to low levels of sarin and cyclosarin during and after the war, and recent research findings indicating that low-level sarin exposures can result in chronic health sequelae, the Committee concludes that low-level exposure to chemical agents must be thoroughly investigated as a potential contributing cause of the multisymptom illnesses affecting Gulf War veterans, and that it is important that the precise mechanisms of chronic adverse effects of low-dose exposures be identified.

Exposure to acetylcholinesterase inhibitors during the Gulf War. As described, DOD estimates indicate that approximately 100,000 Gulf War veterans may have been exposed to low levels of the nerve agents sarin and cyclosarin in association with the Khamisiyah incident. These nerve agents belong to a family of chemical compounds called acetylcholinesterase inhibitors (AChEi), which also includes many types of pesticides and pyridostigmine bromide (PB), the active ingredient in the NAPP pills still used to protect troops from the nerve agent soman. The known toxic effects of AChEi compounds are largely due to their inhibition of an enzyme that breaks down acetylcholine (ACh), one of the major signaling chemicals, or neurotransmitters, in the nervous system. In the presence of AChEi compounds, ACh accumulates in the synapses, or small spaces between nerves. This build-up produces an over stimulation of certain types of nerve cells that can lead to a broad range of immediate symptoms such as muscle contractions, pain, weakness and fatigue, slowed heart rate, tearing, runny nose, excess salivation, nausea, abdominal cramping and diarrhea, respiratory distress, cognitive impairment, and convulsions. Low-level exposures to AChEi compounds can produce relatively mild immediate symptoms, while higher-dose exposures can lead to respiratory failure and death.

While any exposure to nerve agents may be a potential cause for concern, exposure to less toxic types of AChEis such as pesticides are a routine part of life for many who use them in their homes or workplaces. In addition, studies have indicated that therapeutic use of the AChEi pyridostigmine bromide (PB) is generally safe under experimental conditions.^{35,58,88} What has not been conclusively determined is whether PB or pesticides, as used alone or in combination with other neurotoxic compounds during the Gulf War, could have contributed to the chronic illnesses affecting Gulf War veterans.

Long-term effects of pyridostigmine bromide use in the Gulf War are unknown.

[SH], assigned to the 145th Transportation Company, also reported getting very sick from the nerve agent pre-treatment pills. He reported severe nausea and diarrhea that did not abate until he stopped taking the pills after two days. He recalled thinking that "if I'm going to feel like this I might as well be dead." [SH] currently suffers from memory loss, fatigue, sore muscles and joints, insomnia, cough, some night sweats, diverticulitis, diarrhea, kidney stones, bloody stools, urinary urgency, growth on his eye, rashes, tingling and itching sensations, and depression and irritability.

- Report of the Senate Committee on Banking, Housing, and Urban Affairs, May 25, 1994³⁴⁷

Pyridostigmine bromide (PB) is a carbamate drug that temporarily and reversibly inhibits AChE. It has been used since 1955 as a long-term treatment for myasthenia gravis, a chronic disease characterized by progressive muscle weakness. During the Gulf War, PB was classified as an investigational new drug for use as a preventive measure to protect troops from the acute and deadly effects of exposure to the nerve agent soman. Recommended usage was to take one 30-mg. tablet three times per day, at eight-hour intervals. Unit commanders had authority to order when and for how long PB was to be used, but no records are available that documented the actual extent of PB use during the war. In 2000, the RAND Corporation reported the results of a DOD-sponsored survey of pesticide and PB use among 2,005 veterans who had served on the ground during the Gulf War. Investigators estimated, based on survey results, that slightly more than half of in-theater Army, Navy, and Marine Corps personnel took PB pills at some time during the war, and just under one quarter of Air Force personnel. Among those who took PB, median use was about two pills per day for 10 days, although individual use varied, with some individuals reportedly taking considerably larger numbers of pills for extended periods of time.⁸⁴

A detailed review of animal studies that provide information relevant to the efficacy and long-term safety of PB as an adjunctive pre-treatment for nerve agent exposure is beyond the scope of the present report. However, in 1999, the RAND Corporation published a comprehensive review of the scientific literature pertaining to these issues.⁹³ This report, sponsored by DOD, provided detailed analysis of several hypothetical mechanisms that may have lead to heightened or altered PB effects during the Gulf War, as well as mechanisms through which PB might have produced chronic symptoms after the war. The report concluded that, based on available scientific information, PB could not be ruled out as a contributor to Gulf War veterans' chronic unexplained illnesses. Further, the report pointed out that the many questions associated with both the safety and efficacy of PB use as a nerve agent pretreatment require further research and analysis, since decisions regarding this complex issue involve "trading off uncertain

health risks—but risks now shown to be biologically plausible—against uncertain gains from use of PB in the warfare setting.”⁹³

An IOM review of the laboratory, clinical, and epidemiologic scientific literature related to PB, published in 2000, concluded that there was “inadequate/insufficient evidence to determine whether an association does or does not exist between PB and long-term adverse health effects.”¹³⁴ The report pointed out that major areas of uncertainty regarding effects of PB use during the Gulf War include those regarding possible interactions with other agents present in theater that may have affected the pharmacological and toxicological properties of PB and genetic differences in susceptibility to PB.

As previously indicated, PB has been shown to be relatively nontoxic in short-term clinical studies of healthy human volunteers,^{35,88,90,142} although some, usually mild, side-effects of the drug have been noted.^{28,93,134} Higher rates of side-effects have been reported in association with higher PB dosages⁵⁸ and when PB is taken under stressful conditions.²⁶⁵ In a survey of 148 Gulf War personnel conducted in April, 1991, about one third reported experiencing negative side-effects of PB.⁴⁵ A survey of the medical officers who supported the XVIII Airborne Corps during the Gulf War indicated their impressions that about half of those taking PB experienced some type of adverse side-effects, predominantly gastrointestinal symptoms such as loose stools, abdominal cramps, and nausea.¹⁷¹ Several additional small, unpublished surveys of Gulf veterans in theater indicated that between 25 and 37 percent reported side-effects in association with PB use in theater, most commonly gastrointestinal difficulties.⁹³

A number of epidemiologic studies have found that veterans who reported using PB during the war have higher rates of chronic ill health than veterans who did not use PB.^{52,107,138,222,259,349,361} A study of Ohio reservists suggested that a dose-response effect may exist for PB, since veterans who reported taking more PB pills during the war were found to have higher rates of ill health than veterans who reported taking fewer PB pills.²⁶⁰ Of particular interest are results from studies of Gulf veterans that have assessed possible associations between PB and illness using analytic techniques that control for the effects of multiple exposures in the same individuals. Such studies have consistently indicated that self-reported PB use during the war is associated with higher rates of multisymptom illness.^{52,107,222} Also of interest are the results of a 2003 study from the Boston VA Environmental Hazards Research Center, which compared neurocognitive measures between treatment-seeking Gulf War veterans and nondeployed veteran controls. As previously described, the study found that Gulf War veterans scored significantly worse than nondeployed veterans on tests of attention, visuospatial skills, visual memory, and mood. However, when Gulf War veterans were further assessed according to whether or not they had taken PB during the war, or were diagnosed with PTSD, investigators found that those who had used PB scored significantly

worse on tests of executive function, while no association was found between PTSD and cognitive function.²⁹⁴

In summary, the Committee concurs with previous scientific panels in concluding that additional research is needed to determine whether PB use during the Gulf War contributed to the development of the unexplained illnesses in Gulf War veterans. Existing epidemiologic and laboratory studies suggest that such a link is plausible, although little is currently known about the long-term health effects of PB use in wartime, particularly with respect to possible interactions between PB and exposure to other neurotoxic compounds and wartime stressors.

Possible effects of pesticide use during the Gulf War.

Evidence in the literature is suggestive, but not conclusive, that pesticides, specifically AChE inhibitors such as organophosphates and carbamates, could be among the potential contributing agents to some of the undiagnosed illnesses seen in Persian Gulf War veterans.

- A Review of the Scientific Literature As It Pertains to Gulf War Illnesses--Volume 8: Pesticides⁴⁸

The deserts of Saudi Arabia, Iraq, and Kuwait were often extremely inhospitable environments for Coalition troops. In addition to temperature extremes and blinding sandstorms, the desert was home to an assortment of pests that included biting insects, ticks, and rodents. Protection of personnel from desert pests was an important concern for military health and sanitation operations during the Gulf War, charged with minimizing casualties due to pest-borne diseases. Earlier Middle East deployments had been associated with high rates of pest-borne infectious diseases, such as sand-fly fever in World War II.³⁰² To prevent similar problems in the Gulf War, large supplies of insect repellants and pesticides were provided to military personnel. Service members in different branches and in different geographical areas used different types of compounds. Many used DEET cream or liquid on their skin and sprayed long-lasting pyrethroid compounds on their uniforms. Area fogs were regularly sprayed in camp areas to reduce flying insects, while pest strips or aerosols were used in tents. Prisoners of war were routinely sprayed with lindane for delousing purposes and some U.S. personnel reported wearing animal flea collars to ward off biting insects.

Organophosphate (OP) and carbamate pesticides, although not as potent as nerve agents, kill insects in much the same way as nerve agents kill people, by inhibition of AChE. It has long been known that OP pesticide poisoning can cause a chronic neuropathic syndrome.¹⁴⁷ Scientific research regarding possible effects of low-level exposure to pesticides has focused almost exclusively on populations chronically exposed to pesticides by virtue of their occupations or where they live. For example, a 1999 study identified a similar pattern of neuropsychiatric symptoms (memory and attention deficits, impaired muscle strength, personality changes, chemical sensitivity) among farmers and community residents exposed to

organophosphate pesticides.⁶³ Almost no research is available that provides information directly applicable to the possible consequences of subacute pesticide exposures over several months, often in combination with other pesticides and AChEi compounds, as experienced by military personnel stationed in the Gulf War theater.

In April, 2003, DOD issued its final Environmental Exposure Report on Pesticides. That report documented efforts of the Deployment Health Support Directorate to gather information on pesticide use in the Persian Gulf theater of operations, and its potential to have caused adverse health effects. The report determined that 37 individual pesticide ingredients were probably used during the Gulf War, and identified 15 pesticide products to be “pesticides of potential concern,” based on available information about the toxicity and use of the compounds in theater. The identified compounds of highest concern are listed in Table 8.³²¹

In February, 2003, an IOM committee published an extensive report reviewing the scientific literature regarding the potential for specific types of insecticides and solvents used during the Gulf War to have contributed to the chronic health problems experienced by Gulf War veterans. The report focused on evidence regarding exposures to individual pesticides and defined health outcomes and concluded that there is limited/suggestive scientific evidence indicating that OP poisoning is associated with long-term neurobehavioral effects. However, the committee did not find there to be sufficient scientific evidence to determine whether or not OP exposures that do not produce acute symptoms of poisoning were likely to produce neurodegenerative disease such as Parkinson’s disease and ALS, cancer, or reproductive effects. The Committee also reviewed nine studies that evaluated chronic effects of OP exposures at levels not associated with acute signs of toxicity. These studies differed in design and quality, and identified varying degrees of neurobiological deficits in exposed cohorts. As a result, committee members did not reach consensus as to whether there was suggestive evidence or insufficient evidence to indicate that lower-level OP exposures were linked to chronic neurobehavioral effects.¹³⁷

The RAND survey of pesticide and PB use during the Gulf War indicated that two-thirds of service members used some type of personal-use pesticides during deployment, with the proportion varying from 50 percent who reported using DEET a median of 30 times per month to three percent who reported using flea collars while in theater. About half of surveyed Gulf War veterans reported using just one or two forms of personal-use pesticides in any one month, while about 10 percent used three or more forms. The survey also found that pesticide use varied in different veteran subgroups. For example, Army personnel reported the highest level of pesticide use and Air Force personnel the least. In addition, service members who lived in buildings during deployment used lesser amounts of pesticide spray and liquids than those living in the desert.⁸⁴

Table 8. Products Used During the Gulf War Identified by the Deployment Health Support Directorate as Pesticides of Potential Concern

Pesticide	Class	Purpose	Application Method
DEET, 33% cream/stick	Repellant	Repel flies and mosquitoes	By hand to skin
DEET, 75% liquid	Repellant	Repel flies and mosquitoes	By hand to skin, uniform, netting
Permethrin, 0.5% spray	Repellant	Repel flies and mosquitoes	Sprayed on uniforms
d-Phenothrin, 0.2% aerosol	Area spray	Knock down, kill flies and mosquitoes	Sprayed in area
Methomyl, 1% crystals	Fly bait	Attract and kill flies	Placed in pans outside latrines, tents
Azamethiphos, 1% crystals	Fly bait	Attract and kill flies	Placed in pans outside latrines, tents
Dichlorvos, 20% pest strip	Pest strip	Attract and kill mosquitoes	Hung in tents, working areas, dumpsters
Chlorpyrifos, 45% liquid	Sprayed liquid	Kill flies, mosquitoes, flying insects	Sprayed in comers, cracks, crevices
Diazinon, 48% liquid	Sprayed liquid	Kill flies, mosquitoes, flying insects	Sprayed in comers, cracks, crevices
Malathion, 57% liquid	Sprayed liquid	Kill flies, mosquitoes, flying insects	Sprayed in comers, cracks, crevices
Propoxur, 14.7% liquid	Sprayed liquid	Kill flies, mosquitoes, flying insects	Sprayed in comers, cracks, crevices
Bendiocarb, 19% liquid	Sprayed powder	Kill flies, mosquitoes, flying insects	Sprayed in comers, cracks, crevices
Chlorpyrifos	Fog	Kill flies, mosquitoes	Large area fogging
Malathion, 91% liquid	Fog	Kill flies, mosquitoes	Large area fogging
Lindane, 1% powder	Delouser	Kill lice	Dusted on prisoners, also for personal use

Source: *DOD Environmental Exposure Report: Pesticides*³²¹

The RAND survey also identified a significant association between the amount of pesticide used and the number of PB pills taken in a given month. For example, six percent of veterans accounted for the highest level of personal pesticide use in theater, with an average of 120 pesticide applications in a 30-day period. This same group also consumed, on average, 19 PB pills in a 30-day period. In contrast, personnel who reported that they did not use personal pesticides while in theater took an average of only six PB pills per 30-day period.⁸⁴

Based on this and other information, the DOD Environmental Exposure Report on Pesticides concluded that at least 41,000 service members were likely to have been overexposed to pesticides during deployment to the Gulf. The report, the first from DOD to identify a possible contributing environmental cause for veterans' illnesses, stated that "Overexposure to pesticides, particularly organophosphates and carbamates, may have contributed to the unexplained illnesses reported by some Gulf War veterans."³²¹ It recommended that further research be conducted regarding the effects of low-level pesticide exposures and interactions of pesticides with other chemicals, including PB and low-level exposure to nerve agents.

Animal studies evaluating synergistic effects of combinations of Gulf War-related exposures. As previously described, multiple lines of evidence indicate that wartime exposures to different types of AChEi, including nerve agents, PB, and pesticides, may plausibly be linked to the development of chronic illnesses since the Gulf War. It is likely that when veterans encountered these exposures in the Persian Gulf theater, however, it was often in conjunction with other Gulf War-related exposures of potential concern. Studies have shown that different exposures during the war were highly correlated—that is, veterans who report some exposures in theater are also more likely to report other exposures.^{52,84,281} Correlations between multiple exposures are to be expected, since veterans in different locations at different times would likely have experienced similar combinations of exposures. Ground troops located in Iraq, Kuwait, and Northeastern Saudi Arabia during and after the period of active hostilities, for example, would have been most likely to be exposed to SCUD attacks, PB, oil well fires, depleted uranium, and airborne fallout from demolition of chemical targets.

Historically, in comparison to the extensively studied toxicological effects of thousands of individual chemical compounds, relatively little scientific research has been conducted to understand possible adverse health effects resulting from multiple concurrent exposures. In 1996, an important new area of Gulf War-related research was initiated through a collaborative effort between researchers at Duke University and the University of Texas Southwestern. The first published study from this group reported that chickens simultaneously exposed to three neurotoxic chemicals associated with Gulf War service—PB, the insect repellent DEET, and the insecticide permethrin—suffered significant adverse effects, while exposure to similar levels of the chemicals individually produced only minimal toxicity.⁹ These findings were provocative, but also controversial, since the studies utilized exposure dosages higher than those typical of Gulf War service. In the years that followed, however, this research has been broadly extended to include lower-dose exposures to these and other chemical combinations, and in other animal models.

As a result, dozens of studies published by this and other research groups have now consistently demonstrated synergistic effects of different combinations of Gulf War-related exposures, as shown in Table 9. Such studies have identified significantly enhanced toxicities in different

Table 9. Animal Studies Evaluating Synergistic Effects of Gulf War-Related Exposures

Study	Year	Animal Model	Exposures Studied	Major Finding(s)
Abou-Donia ⁹	1996	hen	PB, DEET, permethrin	Neurotoxicity greater when 2 exposures combined, further enhanced when all 3 exposures combined
Abou-Donia ⁸	1996	hen	PB, DEET, chlorpyrifos	Combined exposures enhanced inhibition of brain AChE, BChE, and NTE, neurologic dysfunction, and neuropathologic lesions
Baynes ²⁶	1997	rodent, pig skin	DEET, permethrin, carbaryl	DEET does not enhance dermal absorption of permethrin or carbaryl
Buchholz ⁴¹	1997	rat	PB, permethrin	PB ingestion resulted in lower central nervous system levels of permethrin
Chaney ⁴⁹	1997	mouse	PB, adrenergic drugs, caffeine	Lethality of PB enhanced by adrenergic drugs and caffeine
McCain ²⁰⁰	1997	rat	PB, permethrin, DEET	Significantly greater lethality from combinations of exposures than single exposures
Chaney ⁵⁰	2000	rat	DEET, PB	DEET + PB significantly inhibited brain AChE activity, but not peripheral AChE activity
Van Haaren ³⁵⁰	2000	rat	PB, permethrin	Serum permethrin levels were increased by co-exposure to PB, but the combination did not affect behavioral responses
Hoy ^{126,127}	2000 2000	rat	PB, DEET, permethrin	Permethrin in combination with either PB or DEET affected locomotion rates in male, but not female rats
Abou-Donia ⁶	2001	rat	PB, DEET, permethrin	Combined exposures at physiologically relevant doses led to neurological and behavioral deficits, and alterations in brain AChE receptors
Abou-Donia ⁵	2001	rat	DEET, permethrin	Combined dermal exposures decreased blood brain barrier permeability in cerebral cortex and produced impaired sensorimotor performance
Abu-Qare ¹⁰	2001	rat	Sarin, PB	Combined exposures led to increases in urine levels of markers of oxidative stress
Abu-Qare ¹¹	2001	rat	DEET, permethrin	Single dermal dose of combined exposures produces significant increase in mitochondrial release of cytochrome c
Abu-Qare ¹²	2001	rat	PB, DEET, permethrin	Oral PB combined with dermal application of DEET resulted in maximum urine levels of markers of oxidative stress
Peden-Adams ²³³	2001	mouse	DEET, PB, JP-8 jet fuel	Exposure combination altered selected immunological endpoints, including delayed hypersensitivity and suppression of IgM response, but did not affect other immune measures
Van Haaren ³⁵¹	2001	rat	PB, permethrin, DEET	Small doses of chemicals disrupt behavioral responses, with synergistic effects observed in some measures

Table 9. (cont.) Animal Studies Evaluating Synergistic Effects of Gulf War-Related Exposures

Study	Year	Animal Model	Exposures Studied	Major Finding(s)
Abdel-Rahman ³	2002	rat	Restraint stress, low-dose PB, DEET, permethrin	Combined exposures disrupted blood brain barrier in some brain areas, and led to increased neuronal death
Baynes ²⁷	2002	pig skin	PB, permethrin	PB significantly enhanced dermal absorption and distribution of permethrin
Riviere ²⁵³	2002	pig skin	Permethrin, sulfur mustard, JP-8 jet fuel, DEET	Permethrin absorption and penetration increased by presence of JP-8 fuel, decreased by presence of sulfur mustard
Vogel ³⁵³	2002	mice	DFP, PB, permethrin, parathion	PB reduced DFP binding; permethrin and parathion increased DFP binding in the brain
Abou-Donia ⁷	2003	rat	Stress, PB, DEET, permethrin	Combined exposure to physiologically relevant doses of chemicals caused destruction of testicular germ cells; effect enhanced by stress
Husain ¹²⁷	2003	mouse	Sarin, PB, exercise	Exercise augmented synergistic effects of chemical exposures on AChE activity and NTE activity in various tissues
Riviere ²⁵²	2003	pig skin	DEET, PB, DFP, permethrin, sulfur mustard	DEET absorption enhanced by PB, mustard, and DFP
Scremin ²⁶²	2003	rat	PB, sarin	PB reduced delayed neurological and behavioral effects of sarin, but did not reverse delayed effects on brain muscarinic receptors
Abdel-Rahman ²	2004	rat	Malathion, DEET, permethrin	Combination of pesticides induced neurobehavioral deficits and neuron degeneration, with no overt signs of neurotoxicity
Abdel-Rahman ¹	2004	rat	Stress, PB, DEET, permethrin	Combined exposures produced damage to areas of the brain associated with motor and sensory function, learning and memory, and coordination
Abou-Donia ⁴	2004	rat	PB, DEET, permethrin	Combined exposures produced sensorimotor deficits and altered brain AChE activity levels
Olgun ²²⁹	2004	mouse	Lindane, malathion, permethrin	Exposure of thymus cells to combinations of chemicals resulted in significantly higher levels of apoptosis and necrosis

biological systems and animal models that result from different combinations of Gulf War-related exposures. For example, combinations of DEET, PB, and permethrin have been shown to synergistically increase indicators of neurotoxicity, including changes in brain AChE levels and behavioral changes. Other studies have indicated that absorption of some topically-applied pesticides, such as DEET and permethrin, is increased by concurrent exposure to PB or JP-8 jet fuel. In addition, studies have demonstrated changes in immunological function that result from exposure

to chemical combinations. Taken as a whole, this body of evidence provides strong support for the contention that combinations of Gulf War exposures may have produced toxic effects that exceed those expected with individual exposures. It is important that research of this nature be continued to allow more precise determination of the mechanisms and pathways affected by multiple co-exposures to toxic agents in the Gulf War. It is also important that synergistic effects of multiple Gulf War exposures be considered in epidemiologic evaluations of risk factors associated with Gulf War veterans' illnesses.

Epidemiologic studies consistently link Gulf War illnesses to AChEi exposures. Veterans who served in the Gulf War experienced a unique environment characterized by a complex mix of wartime stressors, disease-bearing pests, and an amalgam of potentially toxic substances. Studies of human populations exposed to low-level AChEi, such as sarin or OP pesticides, are helpful in providing insights regarding potential long-term effects of these exposures individually, and animal studies provide essential information regarding possible synergistic effects of multiple exposures. There is, however, little clinical or epidemiologic research documenting possible long-term health effects of exposure to PB, nerve agents, and pesticide combinations. The only group that can be studied specifically to determine the effects of service in the 1990-1991 Gulf War are the veterans themselves. And, for the majority of Gulf War-related experiences and exposures, the only source of information currently available is to query veterans about characteristics of their wartime service.

Epidemiologic studies of Gulf veteran groups from different states and countries have provided generally consistent descriptions of the types of chronic symptoms reported by ill veterans. Among these studies, a number have evaluated rates of symptoms, symptom complexes, and other measures of ill health in relation to wartime exposures reported by veterans. Studies that have evaluated the risk of veterans' ill health in relation to a long list of Gulf War-related exposures, without controlling for possible errors introduced by the effects of multiple concurrent exposures, typically find that most of the exposures about which veterans are asked seem to be linked with veterans' chronic symptoms.^{138,349} However, studies that analyze risk factors for Gulf War illnesses more precisely by using techniques that control for confounding effects of multiple exposures, consistently find that a more limited number of wartime exposures are associated with higher rates of illness.

Epidemiologic studies have assessed both ill health and wartime exposures among Gulf War veterans in different ways. As shown in Table 10, however, these studies have consistently identified AChEis to be significantly associated with higher rates of symptoms and illnesses in Gulf War veterans. The uniformity of these results contrasts with a lack of consistent findings in multivariable analyses for such wartime experiences as participation in combat, exposure to oil fire smoke, and exposure to depleted uranium. Limitations in epidemiologic studies that rely on self-reported exposures always require a cautious interpretation of findings.

Table 10. Population Studies Assessing Relationships of Multiple Exposures in Theater to Gulf War Veterans' Illnesses

Population Studied	Sample Size	Health Measure	Association with Self-Reported Exposures		
			Chemical Weapons	PB	Pesticide Use
*Air Guard veterans ²²²	1,002	severe CMI	+	+	+
		mild/moderate CMI	+	+	+
*Army veterans from New England, New Orleans ²⁴⁴	291	neurological and musculoskeletal symptoms	+	--	+
Australian veterans ²⁴	1,456	functional impairment	+	+	+
Iowa veterans ¹³⁸	1,896	cognitive dysfunction	+	+	+
*Navy Seabees ⁹⁸	11,868	CMI (modified)	+	+	+
*Navy construction battalion ¹⁰⁷	249	1 or more of 3 defined syndromes	+	+	+
*New England Army veterans ³⁶¹	1,290	CMI (modified)	na	+	na
*Pacific Northwest veterans ²⁸¹	354	unexplained illness	--	+	+
UK male veterans ³⁴⁹	2,735	CMI (modified)	+	+	+
*UK veterans ⁵²	7,971	symptom severity	na	+	+

CMI: chronic multisymptom illness as defined by Fukuda et al.⁸⁵

+ : statistically significant association; -- : association not statistically significant; na: association not assessed

* Indicates analyses controlled for possible confounding due to concurrent exposures

However, the overall consistency of epidemiologic findings indicating higher rates of ill health in association with AChEi exposures, as reported by multiple studies using different methods and different populations, provides compelling support for a role of AChEis in the development of Gulf War veterans' illnesses.

Differences in enzymes that metabolize AChEi may predispose some individuals to greater vulnerability to neurotoxic exposures. As shown in Table 10, epidemiologic studies have consistently implicated exposure to AChEi compounds such as chemical nerve agents, PB, and pesticides as risk factors for Gulf War veterans' illnesses. Additional research that strongly supports a causal role for AChEi exposures comes from a group of studies that have identified differences between ill and healthy Gulf War veterans in blood levels of enzymes used by the body to counteract the toxic effects of these compounds.

An important question concerning wartime exposures and Gulf War veterans' illnesses relates to the reasons why some veterans returned from theater with chronic symptoms, but others with similar exposures did not become ill. Answers to that question may relate to differences in individual susceptibility to the effects of some toxic exposures. Such differences could relate to different doses and combinations of exposures experienced by different individuals in theater. They might also arise from differences between individuals in their ability to clear the body of neurotoxic substances, due to biological differences in the enzymes that metabolize those compounds.

In 1999, investigators from the University of Texas Southwestern reported that ill Gulf War veterans had significantly reduced activity levels of paraoxonase (PON1), an enzyme that metabolizes, and thus inactivates, AChEi compounds.¹⁰⁴ The most severely symptomatic Gulf veterans in the Texas study exhibited particularly low activity of PON1 type Q, the type most active in neutralizing the effects of the nerve agents sarin and soman.⁶⁴ Veterans with low PON1 type Q activity were also more likely to have suffered acute adverse reactions to PB in theater. The following year, researchers from the United Kingdom reported that British veterans with Gulf War syndrome had significantly lower PON1 activity levels than matched healthy controls, independent of the specific PON1 genotype of the veteran. These investigators also concluded that veterans' decreased capacity for metabolizing AChEis may have contributed to their development of Gulf War illnesses.¹⁹³ However, a second study of British Gulf War veterans found that lower PON1 activity was not linked with ill health in Gulf War veterans, but was significantly lower, overall, among veterans who served in the Gulf War than in veterans who did not deploy to the Gulf.¹²³ Taken together, these findings provide a consistent indication that differences in PON1 enzyme activity may be associated with Gulf War illnesses, or perhaps more generally with service in the Gulf War. However, the precise ways in which PON1 differences observed in Gulf War veterans may be linked to genetically-determined factors and/or Gulf War-related exposures remain unclear.

Putative roles for other metabolizing enzymes have also been suggested as possible explanations for why some veterans may have been more vulnerable to the effects of neurotoxic exposures than others. In 1995, investigators from Jerusalem described the case of an Israeli soldier who carried an atypical gene for the enzyme butyrylcholinesterase (BChE), known to be a scavenger for some cholinesterase-inhibiting compounds.¹⁹⁰ Carriers of this gene are unable to metabolize a muscle relaxant commonly administered during surgery,¹⁸⁷ and are also thought to be hypersensitive to some AChEi insecticides.^{81,189} This Israeli soldier suffered severe symptoms after receiving PB during the Gulf War. After conducting laboratory tests, investigators determined that his BChE was less able to bind with, and thus detoxify, PB and other AChEis, likely making him more susceptible to the toxic effects of these compounds. In a related unpublished report from a DOD-sponsored study, investigators from the University of Nebraska Medical Center found that relatively rare genetic

variations of BChE were identified disproportionately among Gulf veterans who reported being sick with Gulf War illness, compared to veterans who did not have these symptoms.¹⁸⁸ The University of Texas Southwestern study also found that ill Gulf war veterans were more likely to have genetic variants and low activity levels of BChE, although these associations were based on small numbers and did not reach statistical significance.¹⁰⁴ Findings from these reports are preliminary and should not be over-interpreted. But they do signal the need for further elaboration of possible linkages between BChE genotype and Gulf War veterans' illnesses.

In related research sponsored by DOD, Israeli investigators have identified a mechanism through which exposure to AChEi or acute psychological stress leads to over-production of a normally rare variant of AChE, labeled AChE-R.^{168,169,280} Over-production of this enzyme has been associated with altered cognitive and behavioral function in animal studies,⁵⁵ and with symptoms of fatigue in myasthenia gravis.³⁸ Therapeutic interventions have been developed to counteract these effects, with preliminary promising results.^{38,271,279} The Committee looks forward to reviewing the results of a recently initiated VA study that will determine whether Gulf War veterans' illnesses are associated with overproduction of AChE-R.^{278,364}

Summary of evidence regarding a probable link between exposures to neurotoxins and Gulf War veterans' illnesses.

Objective indicators of neurological impairment and disease, and excess neurological symptoms in Gulf War veterans require a thorough consideration of possible causes for these problems. Government reports have described the extent to which Gulf War veterans were exposed to a variety of potentially neurotoxic substances during their deployment to Southwest Asia. These include low-level exposures to sarin and cyclosarin, consumption of varying amounts of PB tablets, and use of varying amounts and combinations of insect repellants and insecticides. Many of these neurotoxic compounds exert their effects by inhibiting the action of a single enzyme that regulates acetylcholine, one of the most important signaling chemicals in the nervous system. Multiple lines of human and animal research indicate that these substances have the potential to cause long-term health effects similar to those experienced by Gulf War veterans. Animal research has also demonstrated that some combinations of Gulf War-related exposures can lead to adverse effects that significantly exceed those resulting from single exposures. Numerous epidemiologic studies of Gulf War veterans have consistently found higher rates of unexplained symptom complexes to be linked to self-reported use of PB and pesticides, and to possible exposure to chemical agents in theater. Several studies have also indicated that Gulf War illnesses occur disproportionately among veterans who might be more susceptible to the toxic effects of AChEi, due to biological differences in blood enzymes that inactivate these compounds.

Each area of research described, taken alone, provides an intriguing indication that exposure to AChEi compounds may have contributed to the

development of chronic symptoms during and after the Gulf War. Taken as a whole, however, this accumulated body of research provides compelling evidence of a probable link between neurotoxic exposures in the Gulf War and the development of Gulf War veterans' illnesses.

**Finding 4
Recommendations**

The Committee recommends that the federal government expand research efforts to systematically investigate the chronic effects of exposure to neurotoxins encountered during the Gulf War, particularly acetylcholinesterase inhibitors such as sarin, pyridostigmine bromide, and carbamate and organophosphate pesticides. Studies that identify the specific pathways involved in adverse consequences of AChEi exposure and utilize objective biological markers of exposure sequelae are particularly important, as are studies that identify pathways amenable to therapeutic intervention. Specifically, the Committee recommends that VA:

- Establish a comprehensive research program to investigate persistent and/or delayed effects of exposure to AChEi, including sarin and other nerve agents, at dosages comparable to those that may have been encountered in the Gulf War. Such research should focus on elaboration of the specific physiological pathways involved in possible adverse consequences of these exposures, including those involved in synergistic effects of combinations of neurotoxic exposures.
- Work with scientists with appropriate expertise to comprehensively evaluate the role of differences in genotype and activity levels of enzymes such as paraoxonase, acetylcholinesterase, and butyrylcholinesterase, which are associated with the uptake and metabolism of neurotoxins, in susceptibility to wartime exposures and the development of Gulf War veterans' illnesses.
- Give priority to research studies designed to identify and utilize objective biological markers associated with the effects of exposure to AChEi. Such measures might pertain to effects in the brain or in peripheral areas influenced by acetylcholine such as the neuromuscular system, the gastrointestinal system, and the immune system.
- Give priority to research studies capable of identifying pathways involved in chronic adverse effects of AChEi exposure that may be amenable to treatment interventions.
- Expand VA and collaborative research efforts that capitalize on new technologies capable of identifying low-level residues of exposures, their metabolites, or persistent alterations in metabolism or genetic expression resulting from wartime exposures or associated with chronic unexplained illnesses in Gulf War veterans.

Finding 4

- Analyze data from existing and future epidemiologic studies to reevaluate the association of combinations of neurotoxic exposures with chronic illness in Gulf War veterans.

The Committee recommends that the Department of Defense (DOD):

- Make available to researchers studying Gulf War veterans' illnesses detailed information concerning the locations and dates of incidents involving destruction of chemical targets during and after the Gulf War.
- Continue and expand research efforts that identify possible chronic effects of low-level exposure to sarin and other nerve agents, pesticides, and pyridostigmine bromide, individually and in combination.

Finding 5

Finding 5
Other wartime exposures may also have contributed to Gulf War veterans' illnesses.

A variety of exposures potentially encountered by military personnel in the Persian Gulf theater have been suggested as possible causes or contributors to Gulf War veterans' illnesses,^{130,132,215,221,240} as shown in Table 11. Because studies have consistently demonstrated that psychological factors do not adequately explain the symptoms experienced by the majority of ill veterans, the Committee concludes that other plausible causes for these conditions—that is, a broad range of Gulf War-related exposures—must be thoroughly evaluated as possible contributors to the development of veterans' illnesses.

Table 11. Exposures Suggested as Possible Contributors to Gulf War Veterans' Illnesses

Chemical weapons	Depleted uranium
Biological weapons	Oil well fire smoke
Pyridostigmine bromide	Diesel fuel, jet fuel
Pesticides	Sand, dust
Insect repellants	Contaminated water, food
Individual or multiple vaccines	Infectious agents
Antibiotics, antimalarials	Chemical agent resistant coating

Committee deliberations have thus far focused primarily on the role of neurotoxicants and neurological pathology in Gulf War veterans' illnesses. Additional studies and reports have suggested that other Gulf War-related exposures may be implicated in the etiology of these conditions. The most consistent epidemiologic findings come from studies linking multisymptom illnesses in Gulf War veterans to receipt of vaccines. The number and types of vaccines administered to Gulf veterans have been described in detail.^{132,134,311} Military personnel routinely receive a number of inoculations when they first enter service and prior to overseas deployments. Even under the best circumstances, a small proportion of individuals receiving vaccinations can be expected to experience adverse reactions. Such reactions are typically transient and mild, but can sometimes be chronic, serious, or even deadly.¹⁴³

Information concerning a possible link between vaccines and chronic symptoms in Gulf veterans comes from multiple sources.^{22,23,256,342} Population-based studies have consistently found that immunizations reported to be received by Gulf veterans are associated with higher rates of multisymptom illness.^{24,52,94,120,195,261,349} These include findings of excess illness in Gulf War veterans associated with particular types of vaccines, the number of vaccines received, and the number of vaccines received after veterans' arrival in theater.

Particular concern has focused on the anthrax vaccine administered to a reported 150,000 U.S. troops during the Gulf War, as well as to British, Canadian, and Australian personnel. Assessing possible associations between Gulf veterans' illnesses and their receipt of anthrax and botulinum toxoid vaccines has been particularly challenging in studies of U.S. Gulf War veterans, since many units did not record information on these vaccines in the shot records of personnel. A number of potential problems with the anthrax vaccine have been suggested, including problems with quality control during the manufacturing process,^{335,339} changes in the manufacturing process that may have resulted in increased levels of active antigen,³⁴¹ and the use of unapproved adjuvants to bolster the immunological reactivity of the vaccines.^{23,340} Reports have indicated that the anthrax vaccine administered during the Gulf War, commonly referred to as AVA (anthrax vaccine adsorbed) is associated with a relatively high rate of acute adverse reactions,³⁴² and have pointed out that there is insufficient evidence to determine whether the AVA vaccine formulation may be associated with long-term health sequelae.^{134,339}

Anecdotal reports have suggested that symptoms similar to those reported by Gulf veterans have also been reported by civilians who worked in the Persian Gulf theater and by Gulf War era veterans who received vaccines in preparation for deployment to Desert Storm but were never actually in theater.³⁴⁶ One epidemiologic study has reported an excess of symptoms among veterans who did not serve in theater but reported receiving shots from the military during the time of Desert Shield and Desert Storm.²⁸⁵ If chronic multisymptom illnesses were found to be associated with vaccines received by individuals who received the same shots as Gulf War veterans but experienced no other Gulf War-related exposures, a reasonable hypothesis would be that these vaccines also contributed to Gulf veterans' illnesses. However, no studies have been published that have evaluated the rates of chronic multisymptom illnesses among civilians present in theater during the Gulf War, or among military populations who received AVA in the years following Desert Storm. In short, a number of important questions have been raised concerning the potential for vaccines to have contributed to Gulf War veterans' illnesses. Many of these questions can be answered with relatively straightforward studies, but have not yet been addressed by government research.³⁴⁰

Unanswered questions relating to vaccines are just one example of the importance of further studying a variety of exposures for their potential role in Gulf War veterans' illnesses. Scientific reviews commissioned by federal agencies have often indicated that there is insufficient scientific evidence to determine whether exposures encountered in the Persian Gulf theater are likely to be associated with chronic health problems such as those experienced by Gulf War veterans.^{48,93,134,137} The majority of exposures investigated thus far have been neither conclusively ruled in nor ruled out as having contributed to veterans' chronic symptoms.

A major concern that has not been adequately addressed by studies of ill Gulf War veterans or by previous review panels is the potential for

combinations of exposures to have produced adverse effects that do not typically occur when exposures are experienced individually. As previously described, animal studies have consistently shown that some Gulf War-related exposures can act synergistically, producing significantly enhanced levels of toxicity when combined (see Table 9).

Scientific questions regarding the nature and development of chronic symptoms after service in the Gulf War are extremely complex. It is important that research studies attempting to address these questions include hypotheses that recognize that the multiple overlapping symptom complexes observed in Gulf War veterans may have resulted from different individual exposures or different combinations of exposures in different veteran subgroups. Research studies that do not take into account these factors may be incapable of identifying associations that may exist between Gulf War-related exposures and veterans' symptoms.

The Committee recognizes that the lack of specific exposure information for individual veterans presents a challenge to those charged with understanding the specific causes of Gulf War veterans' illnesses. Yet, discerning the causes of Gulf War illnesses is of fundamental importance to understanding the pathophysiological underpinnings of these conditions, identifying effective treatments, and preventing similar problems from occurring in future deployments. The Committee believes that the use of multiple research approaches such as epidemiologic investigations of subgroups of Gulf veterans with known differences in deployment experiences and exposure histories,^{112,288} in conjunction with appropriate clinical and laboratory research, can shed considerable light on the likely relationships of Gulf War illnesses to exposures.

**Finding 5
Recommendations**

In the coming months, the Committee will investigate in greater detail evidence relating to the potential for a variety of exposures encountered during the Gulf War to have contributed to veterans' illnesses. Future reports will include reviews of research related to exposures in theater such as infectious diseases, depleted uranium, oil well fire smoke and other petroleum products, and a more detailed consideration of evidence relating to vaccines. At this time, the Committee recommends that VA:

- Support research efforts that investigate well-evidenced hypotheses concerning potential linkages between Gulf War veterans' illnesses and wartime exposures, including possible chronic effects of combinations of Gulf War-related exposures.
- Work with federal agencies (Centers for Disease Control and Prevention, National Institutes of Health, Department of Defense) involved in conducting vaccine trials that include administration of anthrax vaccine adsorbed (AVA) to ensure that these trials include follow-up assessments of study subjects a minimum of five years after inoculation. Such studies should utilize methods and instruments

Finding 5

capable of capturing chronic symptoms and cognitive difficulties similar to those experienced by Gulf War veterans.

- Conduct a retrospective cohort study that compares chronic symptoms and diagnosed conditions experienced by veterans who received AVA as part of the military's mandatory anthrax vaccination program to those of a comparable group of veterans who did not receive this vaccine.

Finding 6

The health of Gulf War veterans must be carefully monitored to determine if Gulf War service is associated with excess rates of specific diseases, disease-specific deaths, or overall mortality.

Epidemiologic studies have provided preliminary indications that, in addition to excess rates of undiagnosed symptom-defined illnesses, Gulf veterans may also suffer from elevated rates of diagnosed medical conditions such as migraine headaches and respiratory and gastrointestinal conditions (see Table 2). However, definitive studies to determine whether Gulf veterans are at increased risk for clinically diagnosed conditions other than ALS have not been conducted. Also unknown is whether service in the Gulf War may eventually be linked to diseases that take many years to develop.

With diseases of long latency, particularly cancer but also some neurological diseases, any effect of exposure in the Gulf War is not likely to become apparent for at least 10 years after deployment. Therefore, the most critical period for monitoring rates of morbidity and mortality for such conditions is just beginning. The concern that service in war can be linked to specific diseases that do not become apparent for many years is not unprecedented. Studies of U.S. veterans of previous wars have found elevated rates of specific conditions not conclusively identified until decades after the war. For example, the IOM first determined in 2000 that there was evidence that Agent Orange exposure was linked to an increased rate of diabetes in Vietnam veterans, more than 25 years after the end of the war.^{135,327} Veterans exposed to ionizing radiation following the use of the atomic bomb during the occupation of Japan in 1945 and 1946 were first granted compensation for radiation-related cancers in 1988, over 40 years after those exposures.³²⁶

Epidemiologic studies of death rates among Gulf War veterans and nondeployed military personnel initially found that Gulf War service was associated with increased mortality due to accidental causes, but lower death rates from natural causes.^{153,192} Such findings suggested that the lower rate of disease-related mortality observed in Gulf veterans could be due to a “healthy warrior” effect of deployment, with those who deployed being generally healthier than those who had not.¹⁰² More recent U.S. mortality studies report death rates among Gulf War era veterans through 1997, covering a period of seven years, and indicate that differences in death rates associated with Gulf War service have begun to moderate. That is, rates of disease-related deaths have become more similar in Gulf and nondeployed veterans, as have rates of accident-related deaths.^{154,301} Therefore, any “healthy warrior” effect that may have occurred in the early years after the Gulf War appears to have diminished over time. As a result, it may now be possible to more accurately identify any differences that may exist in disease-related mortality related to Gulf War service. For this reason, and because mortality due to diseases with long latency periods might just now be apparent, it is very important that frequent, detailed analyses of mortality data be carried out, and that results of these analyses be made public.

As previously described, existing studies comparing Gulf veterans to nondeployed era veterans have identified relatively few conditions for which Gulf veterans have been hospitalized at rates higher than those found

in comparison populations. Hospitalization studies of Gulf veterans, however, must be interpreted with caution. In general, such studies were limited in their ability to detect excess rates of conditions affecting individuals no longer in the active component of the military.¹⁰² Hospitalization studies would also not be expected to identify excess rates of the types of conditions most commonly associated with Gulf War service, such as migraines, skin conditions, digestive disorders, neurocognitive impairment, and undiagnosed multisymptom illnesses, which are not generally associated with hospitalization. And, more obviously, these studies all have been conducted at a point in time too early to detect excess rates of illnesses such as cancer that can take many years to become clinically apparent.

Studies that found Gulf War service to be associated with a significantly elevated risk of ALS were first undertaken in response to veterans' concerns regarding an apparently large number of ALS cases among relatively young Gulf War veterans.^{103,117} Similar concerns have been raised by veterans regarding other neurological conditions, such as multiple sclerosis (MS) and related demyelinating conditions, Parkinson's Disease, and brain cancers.²⁰⁹ However, no formal studies investigating the prevalence of these conditions in Gulf War veterans have been conducted.

Epidemiologic studies have suggested that environmental exposures similar to those encountered during the Gulf War are associated with an increased risk of chronic neurological diseases with variable latency periods.^{40,71,74,203} Identification of any serious medical conditions that may occur disproportionately in Gulf War veterans is important for a number of reasons, most essentially for alerting veterans to possible health risks and available services. Veterans affected by any condition found to be associated with Gulf War service can, in turn, be further evaluated to provide additional information on etiologic factors that may have contributed to the development or progression of that condition. Gulf War veterans with ALS have reported anecdotally, for example, that a significant exposure to pesticides years after their return from Desert Storm seemed to be associated with the onset of the severe symptoms that ultimately led to their being diagnosed with ALS.^{146,346}

A subset of the symptoms reported by Gulf veterans with unexplained illnesses are similar to those reported in the early stages of some neurodegenerative diseases. For example, early symptoms of MS can include numbness and tingling in the extremities, balance abnormalities, fatigue, mood and cognitive changes, vision problems, and muscle weakness—all symptoms commonly reported in studies of Gulf War veterans. Multiple studies have also reported that Gulf veterans report excess rates of tremors of the extremities,^{51,138,285,349} which can be an early presenting symptom of Parkinson's disease. A number of preliminary findings suggest other possible similarities between Gulf War illnesses and Parkinson's disease. For example, abnormal brain dopamine production, a defining feature of Parkinson's disease, has also been found in a subset of highly symptomatic Gulf veterans.¹⁰⁵ Two neuroimaging studies have

found abnormalities in the basal ganglia region of the brains of symptomatic Gulf veterans,^{109,205} a region also affected in Parkinson's disease.^{33,224} Further, variations in genotype and levels of the enzyme paraoxonase (PON1) have been reported in several studies of Gulf veterans.^{104,193} In particular, a predominance of the R variant at PON1 position 192 has been identified both in symptomatic Gulf veterans,¹⁰⁴ and in Parkinson's disease patients.¹⁷⁷

The occurrence of specific diseases among Gulf War veterans can be monitored in a number of ways. Clinical and hospitalization information on Gulf War veterans from allied countries where healthcare is primarily obtained through a single provider would be particularly helpful in this regard. However, general trends reflecting increases in specific conditions can be assessed through ongoing surveillance activities using databases maintained by the DOD, the Veterans Health Administration (VHA), the Veterans Benefits Administration (VBA), and the Social Security Administration (SSA). Such data can be used to identify "red flags" that signal whether rates of hospitalization, clinic visits, benefits claims, or deaths due to specific conditions appear to be occurring at abnormally high rates in this cohort, relative to veterans who did not deploy to the Gulf War.

Such an approach was utilized by clinical researchers at the Detroit VA Medical Center who, after noticing an excess of gallbladder disease among their young Gulf War veteran patients, obtained data maintained by VA's National Surgical Quality Improvement Program (NFSQIP). Preliminary analyses indicated that the rate of gallbladder disease requiring cholecystectomy increased significantly between 1992 and 1997 among Gulf War veterans, while rates in other veteran groups declined.²⁰⁶ Researchers concluded that this increase could have resulted from abnormal bile emptying secondary to autonomic dysregulation in Gulf War veterans, although their preliminary findings were never formally pursued. These observations deserve further consideration, in light of recent findings indicative of autonomic dysfunction in Gulf War veterans. In addition, the approach used by these investigators provides a useful example of the potential utility of monitoring VHA data to identify conditions that may be occurring at elevated rates in Gulf War veterans.

Formal epidemiologic studies are required to conclusively determine whether or not Gulf War veterans are affected by excess rates of specific conditions, particularly when the conditions in question are relatively rare, difficult to diagnose, or not typically associated with service-connected benefits or premature death. Population-based studies that include appropriate comparison groups are needed to assess the incidence and prevalence of diseases and conditions of particular concern, such as those associated with neurological abnormalities. Such studies should assess disease rates in epidemiologically important veteran subgroups, such as veterans who served in specific areas or who have specific exposure histories. Similarly, if additional conditions of potential concern are identified through ongoing health data monitoring activities, formal studies

will be needed to assess the rates of those conditions in Gulf War veterans and appropriate comparison groups.

The possibility of links between Gulf War service and the development of serious neurological diseases increases the urgency of implementing research studies and surveillance activities necessary to address these concerns. It is important that priority epidemiologic studies and data-monitoring activities be implemented as soon as possible in order to optimize strategies for prevention, early intervention, and treatment of any Gulf War-associated conditions that may be identified through such activities.

Finding 6 Recommendations

The Committee recommends that rates of medical conditions and disease-specific mortality among Gulf War veterans be regularly assessed and reported, and that studies be undertaken to actively identify veterans with conditions of particular concern. Specifically, VA should:

- Continue to identify ALS cases among Gulf War veterans, and evaluate the potential role of toxic exposures encountered in theater or after the war in the development or progression of this disease. Publish findings regarding any identified risk factors for ALS in Gulf War veterans, and provide this information to veterans.
- Undertake epidemiologic studies to determine the prevalence of other serious neurological conditions, including multiple sclerosis (MS), Parkinson's disease, and brain cancers, among Gulf War veterans in relation to appropriate comparison groups. Studies should include ascertainment of the number of cases of rare and difficult-to-diagnose neurological conditions that may have clinical similarities to recognized conditions such as ALS, MS, or Parkinson's disease, but are difficult to precisely characterize.
- Analyze and make available mortality data for U.S. Gulf War and nondeployed Gulf War era veterans every 18 months. Data should be analyzed for a wide range of ICD-9 categories and the results made publicly available, electronically and through published reports. Data already available, covering the period 1998 through 2003, should be analyzed and published immediately.
- Utilize troop location information and data collected in VA's National Health Survey of Gulf War-era Veterans and their Families to assess mortality among subcategories of Gulf War veterans grouped by exposure, location, and demographic and military characteristics. Analyses of mortality rates among Gulf War veterans that do not take into account differences in deployment experiences and exposures could mask even large mortality excesses associated with conditions encountered by a minority of those deployed.

- Regularly monitor information contained in VA clinical and benefit claims data sources and provide annual reports of morbidity and mortality by available diagnostic categories. Age and sex-adjusted rates of hospitalization and benefits claims should be compared between Gulf War and nondeployed Gulf War era veterans, and across military subgroups identifiable through available data.
- Recognizing that assessment of morbidity is difficult for U.S. veterans, for whom health care is not universally available from a single provider, explore the possibility of examining morbidity patterns in allied countries where such data are available. This information may help to identify excesses in chronic diseases before they become apparent using U.S. mortality data or the recommended surveillance activities.
- Where surveillance of clinical or mortality data indicate a possible elevated rate of any condition in Gulf War veterans, undertake appropriate epidemiologic studies to determine the rate of occurrence of that condition among Gulf War veterans and an appropriate comparison group.
- Where a possible excess of any condition is determined, make efforts to identify individuals with that condition among living veterans, especially in situations where early detection and treatment would be beneficial.

Finding 7
Important questions concerning the health of children and other family members of Gulf War veterans remain unanswered.

Media sources and veterans' groups have reported for many years that children born to Gulf War veterans may have increased rates of birth defects in connection with their parents' wartime service.^{14,30,39} In private and public comments to the Committee, Gulf veterans have continued to voice concerns about having children due to uncertainties about the risk of birth defects. Several studies conducted during the 1990s did not find significantly elevated birth defect rates in children of Gulf War veterans, and thus appeared to provide reassurance in this area. More recently, three large population-based studies have called these preliminary findings into question, indicating that several different types of birth defects may have occurred at higher rates in children of Gulf War veterans than in children of nondeployed Gulf War era veterans. Serious problems still appear, overall, to be very rare, but these studies demonstrate the need for further research in this area.

Questions also have been raised about whether veterans' other family members, primarily their spouses and children, may have experienced higher rates of anomalous health problems since Desert Storm. Preliminary and anecdotal information suggesting this to be the case has been presented in media reports and government testimony.^{82,246,346,347} However, little scientific research has been conducted to determine whether Gulf veterans' family members and other close contacts have experienced higher rates of unexplained symptoms or diagnosed medical conditions than comparison groups. As a result, questions about possible effects of Gulf War service on the health of veterans' family members remain unanswered.

Reproductive outcomes associated with wartime service. A 1994 report prepared by the U.S. General Accounting Office for the U.S. Senate Committee on Veterans Affairs identified 21 "potential reproductive toxicants" that were present in theater during the 1990-1991 Gulf War deployment.³³⁶ Associations between birth defects and maternal toxic exposures have been described in a large number of research studies spanning decades.^{152,270} Paternal exposure to a variety of toxicants has also been linked to birth defects, although mechanisms for these effects are less-well understood.^{53,65,299} In 1996, the IOM determined that there was limited/suggestive evidence that Agent Orange exposure and military service in Vietnam were associated with an increased risk of the development of spina bifida, a disabling birth defect involving failure of the spinal cord to close during the first month of gestation.¹³³ A subsequent VA study determined that women veterans who had served in Vietnam reported a significantly higher number of children born with multiple different types of birth defects than women veterans who had not served in Vietnam. Investigators concluded that the identified excess was not likely due to selective recall or over-reporting of birth defects in this group.¹⁵⁷ Consequently, VA now provides monthly disability allowances, vocational training, and healthcare benefits for children of women Vietnam veterans with a wide range of birth defects,³²⁵ and for children of both male and female Vietnam veterans born with spina bifida.

In response to media reports of an apparently higher-than-normal number of children of Gulf veterans born with birth defects, research studies were undertaken in the 1990s to systematically evaluate birth defect rates in this population. Early studies did not identify significant connections between Gulf War service and children's birth defects,^{17,19,59,234} but limitations in study designs left open the possibility that such a link might exist.³³⁶

The first published study in this area assessed the number of children with birth defects among those born to 52 members of two National Guard units in Mississippi.²³⁴ Three children with major birth defects and two with minor defects were identified, which investigators determined to be in the range of the number expected, based on national figures. Although these results suggested that the particular units studied had not experienced a dramatic excess in the overall rate of birth defects, the small size of the study and lack of a military comparison group prohibited statistical evaluation of rates of specific birth defects. A larger study of the birth records of over 75,000 live births at military hospitals between the years 1991 and 1993 followed.⁵⁹ Investigators concluded that there was no evidence of an increase in the rate of birth defects associated with Gulf War service. But again, these conclusions were questioned on the grounds of study limitations, including reliance on data obtained from birth records (which do not capture information on fetal deaths and infant abnormalities not detected at birth) and the absence of information on births in civilian hospitals.^{60,78,102} Children of veterans who separated from the military after the war, particularly children of veterans who were in poor health, would not be included in such studies. A related study of the same military hospital birth cohort identified a three-fold increase in the risk of Goldenhar syndrome among children born to Gulf War veterans, but the association was not statistically significant.¹⁹ Given the rarity of Goldenhar syndrome, the sample size of over 75,000 births was insufficient to determine whether the observed excess rate in children of Gulf veterans was due to chance.

In 2001, a report from VA's large National Survey of Gulf War-era Veterans and their Families indicated that Gulf War veterans reported a significantly greater number of post-war pregnancies that ended in miscarriages or children born with birth defects than nondeployed era veterans. Among both male and female veterans, elevated rates were reported for all birth defects combined, and for subsets of reported problems considered to most likely represent actual birth defects (that is, excluding developmental disorders, perinatal conditions, and miscellaneous pediatric conditions).¹⁵⁵ These results are summarized in Table 12. Stillbirths, pre-term deliveries, and infant mortality did not differ between deployed and nondeployed veterans in this study.

The primary concern regarding interpretation of these findings is that the apparent excess of birth defects might not represent an actual increase in risk, owing to the self-reported nature of the information. Estimates of an apparent association of birth defects with Gulf War service might have

Table 12. Proportion of Gulf War and Nondeployed Veterans Reporting Birth Defects Resulting from First Live Births after June 30, 1991

	Proportion of Gulf War Veterans	Proportion of Nondeployed Veterans	Adjusted* Odds Ratio (95% C.I.)
<u>Any birth defects</u>			
Male veterans	9.0%	4.0%	2.34 (1.76 - 3.10)
Female veterans	8.7%	3.6%	2.85 (1.62 - 4.99)
<u>Likely birth defects</u>			
Male veterans	5.4%	2.8%	1.94 (1.37 - 2.74)
Female veterans	5.5%	2.3%	2.97 (1.47 - 5.99)
<u>Moderate to severe birth defects</u>			
Male veterans	3.7%	2.1%	1.78 (1.19 - 2.66)
Female veterans	4.0%	1.7%	2.80 (1.26 - 6.25)

*Adjusted for race, age, ground vs. other troops, military component, smoking history, pregnancy history, and year of child's birth

Source: National Health Survey of Gulf War-era Veterans and their Families¹⁵⁵

been inflated if Gulf veterans had a greater tendency than nondeployed veterans to identify or report adverse birth outcomes. Recognizing this limitation, investigators sought to determine the accuracy of veteran-reported birth defect information by reviewing medical records associated with the 206 "likely" birth defects reported in the study. Researchers were able to re-interview veterans and obtain medical records related to 139 (67 percent) of those cases. In an October, 2003, presentation to the Committee, investigators reported that among birth defects for which medical records were reviewed, 88 percent were confirmed. This information was used to generate adjusted estimates of the association of Gulf War deployment with birth defects, based on the rates of confirmed cases. Adjusted estimates supported the study's original findings that overall birth defect rates were significantly higher among both male and female Gulf War veterans than in nondeployed veterans.¹⁵⁶

In 2003, investigators from the Naval Health Research Center published a study representing a massive effort that linked birth certificate data from 1989 through 1993 from the six American states with active birth defect surveillance programs to military service records of Gulf War era veterans.²⁰ Records for 11,961 infants born to Gulf War veterans and 33,052 nondeployed era veterans were identified. Analyses indicated that for children born between 1989 and 1991, conceived *prior* to the war, birth defect rates were similar in Gulf War and nondeployed veterans. However, several types of birth defects were significantly more common among children born to Gulf War veterans in 1992 and 1993, conceived after the war. Children of male Gulf veterans had significantly higher rates of two

cardiovascular defects, tricuspid valve insufficiency and aortic valve stenosis. Female Gulf veterans were significantly more likely to have sons born with hypospadias, a defect of the male urinary tract opening. Researchers pointed out that their ability to detect these differences was made possible only by the comprehensive nature of their study design, which involved active surveillance of birth defects that extended beyond the neonatal period, and included births from both civilian and military hospitals. They also pointed out that the size of their study limited their ability to determine whether less common types of birth defects were associated with Gulf War service.

In 2004, British researchers reported the results of a survey targeting all personnel who had served in the Gulf War from the United Kingdom and a comparison group of veterans who had not served in the war.^{77,194} Results indicated that male Gulf War veterans reported a 50 percent higher rate of all congenital malformations combined, including significantly increased rates of malformations of the urinary and musculoskeletal systems. No significantly elevated rates were found among children of female Gulf War veterans, where analyses were limited by small numbers. Investigators were able to obtain clinical information for about half of the pregnancies identified and, similar to the U.S. survey, found that over 90 percent of veteran-reported conditions were confirmed by medical records. When analyses were limited to malformations for which investigators obtained medical confirmation, previously-identified associations between Gulf War service and birth defects were similar, but somewhat weakened in some instances. This suggests that although increased rates of birth defects in some categories are likely to reflect real differences between Gulf and nondeployed veterans, the magnitude of those differences may have been inflated to some extent by reporting bias. The British study also found that male Gulf War veterans reported a significantly higher rate of miscarriages resulting from pregnancies conceived after the war, compared to nondeployed veterans. No differences were observed in the number of stillbirths reported by the two veteran cohorts.

Additional concerns about reproductive health among Gulf War veterans comes from a recently published study that utilized a military hospital cohort to assess outcomes of pregnancies among women veterans between 1990 and 1992.¹⁸ Pregnancy outcomes for the 415 Gulf War veteran women who became pregnant during the time they served in theater did not differ from those of women who had not deployed to the Gulf. However, conceptions that occurred after Gulf veteran women returned from theater were significantly more likely to result in poor outcomes. Specifically, postwar conceptions included nearly a three-fold increase in the risk of spontaneous abortion and a seven-fold increase in the risk of ectopic pregnancy among Gulf veteran women, after controlling for other factors known to be associated with poor pregnancy outcomes.

Related information of interest comes from studies of pregnancy outcomes and births among local populations in Kuwait and Bahrain. In comparing hospital records from the years since the war to those from the

pre-war period, such studies have found post-war increases in the rates of spontaneous abortions, low birth weight babies, and congenital heart disease, particularly in the period immediately following the war.^{13,196,197,247}

Overall, the issue of birth defects and other adverse reproductive outcomes potentially associated with Gulf War service has been the subject of much concern and debate. Three broadly representative population-based studies from different investigators and populations have now indicated that Gulf veterans may have experienced higher rates of some adverse reproductive outcomes than nondeployed veterans since the war. Yet fundamentally important questions remain. The specific types of birth defects linked to Gulf War service have varied in different studies, as have the magnitude of identified risks. Data from survey-based studies indicate that, overall, there appears to be grounds for concern that Gulf War service may be associated with elevated rates of miscarriages and for the total number of all types of birth defects combined. Increased risk both for miscarriages and for the overall number of birth defects since the war, while significant, are rather modest, with odds ratios in the range of 1.5 to 2.0.^{77,155} However, relative risks for some specific types of birth defects identified in the six states with active birth defect surveillance are substantially higher.²⁰ No studies in this area have had the capability to conclusively determine whether less common types of birth defects may be linked to Gulf War service. Also lacking is information on whether adverse reproductive outcomes are of greater concern in particular veteran subgroups, such as those who served in particular areas, experienced specific exposures, or have been chronically ill since the war. Further, existing research studies have focused primarily on birth defects occurring in the early years after the war, with relatively little information on outcomes in more recent years.

The Committee concludes, therefore, that currently available information is insufficient to provide a clear understanding of the extent to which Gulf War service may be associated with an increased rate of birth defects, nor of the specific types of birth defects that may be of concern. While substantial progress has been made in this area in recent years, additional research is needed to address pressing questions to which veterans and their families deserve answers.

Health of other family members of Gulf War veterans. Children born since the war are not the only family members about which Gulf veterans have expressed concerns. Media and government reports have suggested that other family members and close contacts—primarily spouses and children living at home when veterans returned from Southwest Asia—have also experienced increased rates of anomalous health problems since the war.^{82,184,246,346} A 1994 report by the Banking Committee of the U.S. Senate described a survey of 1,200 ill veterans which indicated that 77 percent of veterans' spouses and 68 percent of their children also had experienced unexplained health problems since the war, and that many had symptoms similar to those reported by veterans.³⁴⁷ Such health problems have been variously attributed to contagious infections,²¹⁸

or family contact with contaminated clothing or equipment that veterans brought back from theater.¹⁸⁴ Also perplexing are reports from veterans' wives that they have suffered gynecological pain and other problems resulting from contact with the burning or acidic seminal fluid of their veteran husbands.³¹

While such reports are alarming, questions about the degree to which family members may have been affected by an excess of unexplained health problems can only be answered by research studies that systematically compare the health of Gulf veterans' family members to family members of veterans who did not serve in the region. Surprisingly, despite the many claims and concerns expressed regarding this issue, very little research has been undertaken to evaluate the health of family members of Gulf veterans. For a number of years, VA invited family members of veterans who were on the Gulf War Registry to undergo a free medical examination. This program was reported to have been fraught with problems and inefficiencies,³³⁸ and no public report has ever been issued regarding family member participation or data collected through this effort.

The only federal research study targeting family members of Gulf veterans is part of VA's large National Health Survey of Gulf War-era Veterans and their Families. This study was initiated in 1995 and conducted in three phases. Phase III of the project included comprehensive medical and psychiatric evaluations of a randomly selected group of Gulf War and nondeployed Gulf War era veterans, as well as spouses and children of Gulf War and nondeployed veterans. Exams were performed between 1998 and 2001 in 16 VA Medical Centers across the country. Findings from the study have not yet been published. However, in a 2003 presentation to the Committee, VA investigators indicated that in comparisons between spouses of Gulf veterans and spouses of nondeployed veterans, no significant differences were found in either the primary or secondary health outcomes of interest. These outcomes included chronic fatigue syndrome and fibromyalgia, among other diagnosed conditions.³⁶⁵ Study results are not yet available on conditions other than birth defects in veterans' children.

It is hoped that additional useful information regarding the health of veterans' spouses and children will become available as results from Phase III of the National Health Survey of Gulf War-era Veterans and their Families are analyzed and published. It is important that detailed analyses be conducted that evaluate the health of family members of deployed and nondeployed veterans on a broad range of parameters. Comparisons should be made between family members of the two veteran cohorts overall, and between specific veteran subgroups of interest, including veterans with unexplained symptoms, veterans with other diagnoses, and veterans who had different experiences and exposures in theater. Results from this study will be the first reported in this area, so findings will help determine what, if any, additional studies are needed. Until that time, however, the Committee can only conclude that little systematically-collected

information is currently available to determine whether or not veterans' family members have been affected by an excess of unexplained health problems since veterans returned from the war. In contrast to the multiple large studies investigating birth defects and reproductive outcomes, almost no research has been conducted to evaluate the health of spouses, older children, and other close contacts of Gulf War veterans.

**Finding 7
Recommendations**

Important questions remain concerning the risk of birth defects and other health problems among family members of Gulf War veterans. The Committee therefore recommends that VA:

- Accelerate efforts to complete analyses and publish results from Phase III of the National Health Survey of Gulf War-era Veterans and their Families. Reports should contain comprehensive information on the health of veterans' spouses and children, including an accounting of specific diagnosed conditions, symptoms, and symptom complexes. Special effort should be made to assess childhood health problems or abnormalities not apparent at birth, including learning and behavior disorders.
- Analyze data from existing VA studies to evaluate birth defects and other health measures for family members of important veteran subgroups. Analyses should include comparisons between the health of family members of veterans who are ill and veterans who are well, and comparisons among family members of veterans with different deployment, location, and exposure histories.
- Develop studies with innovative designs to test for excess rates of specific birth defects, such as Goldenhar syndrome, that occur too rarely to address with the types of studies done in the past.
- Continue to query veterans regarding reproductive outcomes and the health of family members in VA's ongoing longitudinal study of Gulf War and nondeployed veterans, and follow up veteran-reported information on birth defects and other health conditions with medical record reviews.
- Issue a public report detailing information and data collected in connection with VA's medical evaluation program for family members of Gulf War veterans.
- Provide clear information to veterans and clinicians concerning what is known about the risk of birth defects related to Gulf War service, and update that information as additional research becomes available.

Finding 8
Progress in understanding Gulf War veterans' illnesses has been hindered by lack of coordination and availability of data resources maintained by the Department of Defense and the Department of Veterans Affairs.

The locations, activities, and exposures experienced by individual veterans who served in the Gulf War were extremely diverse. Likewise, health problems experienced by veterans since the war have occurred in diverse patterns of symptoms and medical conditions. Progress in understanding these conditions requires the availability of an extensive amount of data that allows assessment of health parameters in a large number of Gulf War veterans collectively and in subgroups defined by characteristics of their health and deployment experiences. Scientists and government review panels have consistently pointed out that understanding Gulf War illnesses has been made more difficult by the lack of data on the types and levels of wartime exposures, including vaccines, experienced by individual veterans. But a substantial amount of data relevant to the health, military, and deployment experience of Gulf War veterans currently exists, collected and maintained by DOD and VA. Neither agency, however, has made full use of these data resources and their potential to provide important information regarding Gulf War veterans' illnesses.

A clear understanding of the health of Gulf War veterans, as well as possible links between veterans' health and aspects of their military service, has been hindered by the lack of availability, integration, and usability of data collected by various sectors within the federal government. A large number of datasets currently exist within both DOD and VA that, if properly coordinated and utilized, have the potential to shed considerable light on important questions related to Gulf War veterans' illnesses. For DOD, relevant resources include data on military service dates and service occupations, troop locations and movements during Persian Gulf deployment, in-theater clinic and hospitalization records, locations and dates of Coalition destruction of chemical targets, various exposure measurement and modeling efforts conducted during and after the war, military clinic visits and hospitalizations after deployment, and health and exposure data collected in association with the Comprehensive Clinical Evaluation Program (CCEP). For VA these resources include data from VA's large population-based national survey of Gulf War era veterans, data on medical conditions, laboratory assessments, and treatments associated with VA clinic visits and hospitalizations, diagnostic and treatment data for veterans seen in VA's specialty Gulf War illness clinics, data on benefits claims filed by Gulf War era veterans, and data collected in conjunction with VA's Gulf War Registry.

A pressing need exists for a centralized data resource that would bring together existing datasets relevant to the health of Gulf War veterans. Reconciling and integrating the various federal data resources and making this information available to qualified researchers would allow researchers to better identify meaningful veteran subgroups whose health and military experiences distinguish them from other ill veterans. This information is fundamentally required to sort out the complex illnesses and overlapping symptoms and etiologic factors that together constitute Gulf War veterans' illnesses. Such a resource would also greatly facilitate efforts to monitor the health of Gulf War veterans over time.

Existing studies have indicated that the rates and characteristics of Gulf veterans' conditions differ according to the locations and time periods in which they served in theater. As previously described, a population-based study of Kansas veterans found that Gulf War illness rates were significantly linked to where and when veterans served in theater.²⁸⁵ Other investigations, including a military study of Marines conducted in March, 1991,²⁴² have also reported that symptom profiles and medical conditions among Gulf War veterans differ by the time and locations in which they served.^{72,107,138,198,245} Researchers have called for further refinement and clarification of these findings, pointing out the potential benefits to be gained from information that allows characterization of subgroups of veterans according to where and when they served, the type of units with which they served, and the occupations in which they engaged during the war.^{46,112,288}

Other obvious benefits would be gained by compiling and integrating clinical, registry, and benefits information collected by different departments within DOD and VA, as well as by other federal agencies, such as the Social Security Administration (SSA), which collect data relevant to veterans' health. The ideal scenario would involve complete integration of military, deployment, exposure, and health information from federal data sources to provide a seamless record of veterans' deployment and health experiences during their military service and in the years since the Gulf War.

Currently, the only ongoing effort to compile and monitor data related to the health of Gulf War veterans comes from the Veterans Benefits Administration (VBA). The Gulf War Veterans Information System produces a quarterly report, commonly referred to as the GWVIS Report, which provides summary health and benefits data on all veterans who have served in the military since August of 1990, sub-grouped according to whether or not they served in the Persian Gulf War. This report is useful but limited in scope. It documents the disposition of benefits claims filed by Gulf War era veterans as well as the total number of hospitalizations and deaths identified in this cohort. The GWVIS Report does not provide analytic information, such as comparisons between the proportions of deployed and nondeployed veterans who have filed claims since the war. Nor does it provide information on specific medical conditions for which veterans have been hospitalized or filed claims. However, the GWVIS data team has been extraordinarily conscientious in refining DOD-provided data indicating whether Gulf War era veterans actually served in the Gulf War, and has, as a result, generated a valuable data resource that could be extremely valuable for research purposes and other federal uses. It provides a useful example of utilizing data supplied by DOD, and integrating it with benefits data maintained by VBA and clinical data maintained by the Veterans Health Administration (VHA).

There are other examples in which different data systems managed by VA and DOD have been merged and integrated to address defined research questions for specific projects. These include the prevalence study of

ALS,¹¹⁷ and studies investigating rates of medical conditions, hospitalizations, and mortality in relation to troop locations and proximity to the Khamisiyah weapons demolition and oil well fires.^{61,100, 154,181,273,275, 276}

The integration of datasets in different formats generated by different departments within different agencies for different purposes is a complex and challenging task. The development and management of such a data resource would require a sustained commitment on the part of VA, and a significant level of intra- and inter-agency cooperation. It would also require the adoption of appropriate data management techniques and privacy restrictions to ensure that the data are truly useful and usable.

**Finding 8
Recommendations**

Progress in understanding Gulf War veterans' illnesses would benefit significantly from researchers making full use of data collected and maintained by different departments and agencies within the federal government. The Committee therefore recommends that VA and DOD:

- Cooperate fully in individual projects requiring linkages between specific Gulf War-associated databases, such as the unit location database and healthcare and benefits data, to facilitate the provision of integrated data resources for research purposes.
- Develop a comprehensive data library that houses and integrates federal military, deployment, and health data resources relevant to service in the Gulf War and the health of Gulf War era veterans. This data library would serve as a central data resource capable of providing usable data for the purposes of conducting research on specific questions regarding Gulf War veterans' illnesses and monitoring the health of Gulf War veterans.
- Make federal data resources relevant to Gulf War veterans' health and military experiences available to qualified government and non-government researchers, and adopt appropriate safeguards for the use of these data.

Finding 9
Research on Gulf War veterans' illnesses has important implications for current and future military deployments and for homeland security.

Events associated with the Persian Gulf War and the chronic health problems experienced by veterans since the war have profound implications for military personnel currently serving in the Middle East and for those who will participate in future deployments. Equally important is the relevance of research on the nature and causes of Gulf War veterans' illnesses to considerations related to homeland security and protection from terrorist attack.

Applying the lessons of Gulf War veterans' illnesses to current and future deployments. Many of the concerns related to Gulf War veterans' illnesses are not unique to the Gulf War, but reflect challenges that are increasingly a part of modern warfare. In all times, in all wars, military personnel have faced life-threatening dangers and death from enemy attacks, deadly weapons, and diseases resulting from deployment to hostile areas. Over the years, military and veteran physicians and scientists have developed impressive expertise in addressing the visible wounds and injuries resulting from bullets and bombs, and in supporting veterans suffering from the long-term psychological effects of war. But little progress has been made in addressing another type of health challenge that has affected veterans serving in more recent wars. Such problems arise from exposure to hazardous chemical and biological substances that often do not cause visible wounds or immediate symptoms, but can work insidiously to produce long-term and poorly understood health problems. Military health professionals have been less successful in addressing these conditions, as evidenced by the chronic problems known to have persisted for many years among veterans exposed to chemical agents in World War I, nuclear bomb detonations in the 1940s and 1950s, chemical defoliants in Vietnam, and the complex mix of exposures encountered in Operation Desert Storm.

Although Desert Storm ended in 1991, military operations in the region have continued through the early years of the 21st century. American and allied forces have also served in other war zones around the world in the intervening years, and are now engaged in active hostilities in both Iraq and Afghanistan. Many of the risk factors potentially associated with Gulf War veterans' illnesses continue to be a concern for those serving in these areas. They include the potential for exposure to chemical weapons, depleted uranium, multiple vaccines, infectious diseases and drugs taken to protect against local infections, the use of multiple types and combinations of pesticides, and the use of PB as a protective measure against the nerve agent soman.

Pyridostigmine bromide was classified as an investigational new drug for use in the 1990-1991 Gulf War. As previously described, little is known about the long-term health effects of the use of PB by healthy individuals, particularly under the circumstances in which it was taken during the Gulf War. Animal studies have indicated that PB may act synergistically with other neurotoxins to enhance the effects of those compounds, and scientific and government reports have not ruled out PB as a possible contributor to Gulf War veterans' illnesses. Despite this

information, the U.S. Food and Drug Administration (FDA) approved the use of PB for military personnel as a chemical pretreatment against the nerve agent soman in February, 2003, just prior to the beginning of Operation Iraqi Freedom. As a result, the informed consent requirement and other restrictions that were in place when PB was classified as an investigational new drug are no longer applicable.

Many of the difficulties and delays in the government's response to the chronic health problems affecting Gulf War veterans have resulted from information gaps and incomplete record-keeping related to veterans' health and exposures during deployment. For example, substantial questions remain about the possible contribution of vaccines to Gulf War veterans' illnesses. Evaluation of the contribution of vaccines to these conditions would have been greatly aided by the availability of properly maintained military vaccination records that included specific information on vaccine lots and dosage schedules. Should such problems and questions arise from current and future deployments, VA's ability to identify and treat affected veterans would require access to comprehensive vaccine records maintained by DOD. The lack of such information would again confuse and delay efforts to address possible resulting health problems.

The conditions of war are challenging in innumerable ways, and military operations must emphasize measures that provide for the safety and survival of the soldier on the battlefield above all other health considerations. However, before deployment and after the soldier returns home, it is important that the federal government have in place programs that both minimize the risk of developing illnesses associated with hazardous exposures and address whatever unforeseen health problems may arise as a consequence of deployment.

These responsibilities have been recognized by both DOD and VA. In 1999, the Department of Defense replaced its Office of the Special Assistant for Gulf War Veterans' Illnesses with the Office of Force Health Protection and Readiness.^{174,322} This office has been responsible for programs designed to identify, minimize, and address medical and psychological risks due to occupational factors associated with deployment. VA has also taken a broader approach to understanding and addressing these issues, sponsoring both clinical and research programs that focus on deployment health. Since 2001, VA has sponsored two clinical and research centers that focus on the healthcare needs of veterans who return from wartime service with symptoms and conditions that are difficult to diagnose and treat. These War-Related Injury and Illness Study Centers are located at the VA Medical Centers in Washington, D.C. and East Orange, New Jersey.³³³ The Committee also understands that DOD and VA have worked cooperatively to develop a medical records system that will follow the health of individuals from military recruitment, through military service and deployments, and into the VA healthcare system after discharge.³⁴⁴

The Committee commends these efforts, and urges both agencies to continue to move forward in the continued implementation of programs that minimize deployment-related health risks to military personnel, and more efficiently address unforeseen health consequences of hazardous deployments. It is clear, however, that some important deployment health initiatives with special relevance to the health problems affecting Gulf War veterans have not yet been fully implemented. As a result, there remains a concern that some of the same types of problems, particularly those related to the unavailability of health and exposure information, which delayed progress in the government's response to Gulf War veterans' illnesses, may again affect the government's ability to respond to unforeseen medical consequences of current and future deployments.

To minimize these problems, the Committee concludes that it is extremely important that DOD implement several measures required to prevent and/or more efficiently address future deployment-related health problems. Prominent among these are medical examinations of military personnel before and after deployment that include collection and storage of blood samples. It is also imperative that VA and DOD continue to work together to share deployment information on military personnel, including known hazards encountered in theater, and to finalize implementation of an integrated medical records system that allows personnel to make a seamless transition between DOD and VA healthcare systems.

Research on Gulf War illnesses has broad implications for homeland security and the war on terrorism. Alerts at home and military actions abroad provide constant reminders of the risk of terrorist attack. In the months since September 11, 2001, Americans have been keenly aware that the risk of exposure to chemical and biological weapons and the need for measures that provide protection from their effects is not limited to military populations. In the course of its deliberations on causes of and treatments for Gulf War veterans' illnesses, the Committee has reviewed a large body of evidence related to the effects of chemical weapons, particularly nerve agents, and currently available medical countermeasures against those agents.

Exposures encountered during the Gulf War and research on Gulf War veterans' illnesses provide important insights relevant to the risk of domestic exposure to nerve agents. As previously described, the Department of Defense has estimated that approximately 100,000 Gulf War veterans may have been exposed to nerve agents during the Khamisiyah demolitions in March, 1991, and a recent GAO investigation suggests that the total number of veterans exposed to nerve agents may be much higher.³⁴³ Recent research has called into question the long-held assumption that low-level exposures to nerve agents do not produce chronic adverse health effects. Additionally, the use of pyridostigmine bromide, the "nerve agent pre-treatment pill" taken to protect against nerve agents, may be implicated as a possible contributor to the chronic health problems experienced by Gulf War veterans.

In the last several years, the federal government has made a major commitment to funding medical research programs aimed at defending the public from bioterrorism—that is, the use of biological agents to harm American civilians. The National Institutes of Health (NIH) invested 1.7 billion dollars on research and development programs related to biodefense in fiscal year 2003, 1.6 billion in fiscal year 2004,³²³ and has requested an additional 1.7 billion dollars for biodefense research in fiscal year 2005.³²⁴ NIH has also begun taking steps to initiate research to develop medical responses to nuclear attack, requesting 47 million dollars in funding to develop treatments for nuclear or radiological injuries.³²⁴

Given the appropriate massive national effort to address the possible threat from terrorist use of biological agents, the Committee is concerned that no comparable large-scale program exists that is tasked with developing protection and treatment measures against the effects of chemical agents. No funding dedicated to research in this area has been requested by NIH, and funding for the U.S. Army Medical Research Institute of Chemical Defense, the scientific group historically tasked with sponsoring and conducting research in this area, has actually declined in recent years.²⁶⁹

As the country marshals its medical research resources to defend American citizens against the threat of weapons of mass destruction, it makes little sense to target biological and radiological threats, but leave chemical threats, the easiest and least costly for an adversary to acquire, undefended. This situation is particularly untenable now that recent scientific studies, such as those associated with Gulf War illnesses research, have begun to provide important breakthroughs in understanding the effects of chemical weapons, with significant implications for the development of prevention and treatment measures. In these dangerous times, it is critical that research to pursue these advances and other promising developments be aggressively encouraged and funded.

Some initial steps have been taken within the federal government to provide a preliminary framework for research efforts that address the threat of chemical weapons. In March, 2003, NIH convened a panel of experts “to identify gaps in scientific knowledge about chemical injury and repair, and to identify priorities for the research and development of medical countermeasures.”³⁷⁰ This meeting was followed, in April, 2004, by a workshop sponsored by the National Institute of Neurological Diseases and Stroke for federal government scientists and others “interested in research to develop medical countermeasures against chemical and biologic agents that affect the nervous system and could be used in a terrorist attack.”²¹⁶ The workshop was organized to identify “research gaps of high priority in the area of counterterrorism and neuroscience research,” and attracted broad participation. In addition, the White House Office of Science and Technology Policy has convened a multiagency working group tasked with developing recommendations relating to critical needs in the area of domestic chemical defense. While these initial discussions are useful in laying the groundwork for future scientific and protective endeavors, at

present no programs have been developed and no funding allocated for government research that addresses critical gaps related to medical countermeasures against chemical agents.

As this report is being finalized, Congress has recently passed legislation establishing Project Bioshield, a program that will provide funding to private industry for development of medical countermeasures against biological, radiological, and chemical weapons. The inclusion of chemical threats in this program is a promising initial sign of progress in addressing this issue. It is important that Congress similarly extend NIH's counterterrorism research program to include medical countermeasures against chemical threats.

Finding 9 Recommendations

With respect to the relevance of Gulf War illnesses research to current and future military deployments, the Committee applauds the efforts of the Secretary of Veterans Affairs in encouraging the Department of Defense to maintain comprehensive records of deployment-related health information, including receipt of vaccines, in connection with current military deployments. The Committee further recommends that:

- DOD fully implement the military assessment programs mandated in 1997 by Public Law 105-85, Section 765 (10 U.S.C. §1074f (1997)), which directs DOD to conduct detailed medical examinations of all military personnel before and immediately after deployment to hostile areas, including the collection and storage of blood samples taken before and after deployment.
- DOD take steps to improve record keeping and exposure assessments related to military deployments.
- DOD reassess policies regarding the use of pyridostigmine bromide as a prophylactic measure against the possible effects of nerve agents. This assessment should include a comprehensive review of scientific studies relating to adverse effects of pyridostigmine bromide in combination with other exposures, and revisiting policies concerning the circumstances and decisions that govern orders for the use of pyridostigmine bromide.
- DOD and VA work cooperatively to immediately share information related to current military deployments, including health experiences and exposures in theater.
- DOD and VA continue to work cooperatively to develop and implement a unified health data system that will include all health information of personnel through their military service and transition into the VA healthcare system.

With respect to the relevance of Gulf War illnesses research to preparations against chemical terrorism, the Committee recommends that Congress:

- Establish a comprehensive medical chemical defense research program within the NIH counterterrorism research agenda, and provide adequate funding to field effective medical countermeasures. Enlist in this effort the capabilities of relevant agencies, including the Department of Defense and the Department of Veterans Affairs.
- Expand funding for research programs sponsored by the Department of Defense relevant to chemical defense measures. In particular, continue and expand support for research programs that have provided important information regarding the chronic health effects of sarin and other chemical agents.

Finding 10
Further progress in understanding and treating Gulf War veterans' illnesses requires federal research programs that are properly focused, well-managed, and adequately funded.

Gulf War veterans' illnesses pose a complex challenge—scientifically and administratively—for the federal agencies responsible for addressing them. The U.S. Departments of Veterans Affairs, Defense, and Health and Human Services have worked for over a decade on these problems, individually and collectively, spending hundreds of millions of dollars in research and untold additional funds on clinical care for ailing Gulf War veterans. Despite this massive effort and recent important scientific advances, much remains to be learned about the precise physiological characteristics of veterans' illnesses and the particular exposures or combinations that caused veterans to become ill. Moreover, virtually nothing is known about treatments that can substantially improve the health of ill veterans. Why has so much effort resulted in such limited progress? The Committee believes there are a number of reasons, most having to do with the focus of the federal research effort and the lack of a clear and well-managed program to successfully complete research in areas most important to understanding and treating Gulf War veterans' illnesses.

If progress in addressing Gulf War veterans' illnesses research were to be measured in terms of the number of programs developed, the number of research projects funded, and the number of dollars spent, it might be argued that the federal government has made an admirable effort and considerable progress in undertaking activities to address these conditions. The most recent information compiled by the federal interagency Deployment Health Working Group Research Subcommittee indicates that, in fiscal years 1994 through 2002, federal agencies spent nearly 300 million dollars for research on Gulf War veterans' illnesses in support of 239 individual research projects.⁷³ Certainly, among the many research studies funded by federal agencies, a substantial number have provided valuable information on possible mechanisms of illness and long-term effects of exposures encountered in theater, as well as descriptive information on veterans' symptoms and rates of mortality and hospitalization. As described throughout this report, the Committee commends both the researchers and the federal agencies whose efforts have resulted in important findings concerning the characteristics and physiological nature of Gulf War veterans' illnesses and the long-term effects of exposures encountered in the Gulf War. Many of these scientific findings have only become available in the last few years, as research projects funded in the 1990s have been completed.

However, the Committee is committed to its charge of assessing the progress made in research on Gulf War veterans' illnesses according to another standard—that is, the degree to which this research has improved the health of ill Gulf War veterans. If progress is measured by that central criterion, as well as by broader scientific standards, the Committee finds that the federal research program addressing Gulf War veterans' illnesses has not succeeded in answering fundamental and essential questions regarding Gulf War veterans' illnesses and, consequently, has not succeeded in providing information that has made a substantial difference in the health and lives of ill Gulf veterans.

Planning and coordination of federal research on Gulf War Veterans' illnesses.

A collaborative government-sponsored program has not been established. Evaluation of undiagnosed Persian Gulf illnesses has not followed a uniform protocol across military branches, VA facilities, and civilian physicians. This has led to imprecise description of disease and/or symptoms, uncertainties about underlying prevalence rates, and inconsistent treatments. Well-designed epidemiologic studies have not been conducted to link the illnesses of the military personnel with exposures in the Persian Gulf theater of operations.

- NIH Technology Assessment Workshop Statement, 1994²²¹

Making scientific progress in areas that are poorly understood, as in any endeavor involving achievement of a complex objective, requires planning, coordination, execution, and ongoing evaluation of progress and priorities. Given the multifaceted nature of the exposures and illnesses associated with Gulf War service, it is especially important that the right research questions be asked and the best studies undertaken to answer those questions. In the early stages of addressing a complex research problem, it is important to pursue a broad range of potentially fruitful areas, often including many blind alleys, until scientific breakthroughs point investigators toward research areas most likely to provide significant insights, and away from areas least likely to yield progress. Such an undertaking is challenging in any circumstance, but especially so when it requires the coordinated efforts of several large federal agencies on complex scientific matters with potentially far-reaching political and economic implications.

The lack of scientific progress in addressing Gulf War veterans' illnesses has not been due to a lack of federal initiatives aimed at identifying research priorities. Many of the recommendations provided by the Committee in this report parallel research priorities identified by earlier government review panels and committees. These include recommendations regarding the need to identify effective treatments for Gulf War veterans' illnesses, coordinate federal data resources related to Gulf veterans, monitor the health of Gulf veterans over time, improve assessments of reproductive outcomes, and prospectively collect health and exposure data in association with future deployments.^{130,131,136,221,235,236,240,241,249,304}

The Persian Gulf Veterans Coordinating Board (PGVCB), the federal interagency committee originally charged with coordinating research on Gulf War veterans' illnesses, issued its first comprehensive research plan for addressing these conditions in 1995.²³⁵ The plan identified three central research priority areas:

- Establish the nature and prevalence of symptoms, diagnosable illnesses, and unexplained conditions among Persian Gulf veterans.

- Identify the possible risk factors for any illnesses, beyond those expected to occur, among Persian Gulf veterans.
- Identify appropriate diagnostic tools, treatment methods, and prevention strategies for any excess illness conditions found among Persian Gulf veterans.

Later PGVCB reports expanded on and revised these initial priorities in response to emerging information, such as the release of chemical nerve agents in the Khamisiyah incident. Short and long-term research objectives were established, and 21 priority research questions were identified in the board's 1996 Working Plan for Research.²³⁶ The Board developed an additional set of research priorities in 1998, which included research on treatments for Gulf War veterans' illnesses, longitudinal follow-up of ill Gulf War veterans, and research related to prevention of deployment-related health problems and improved assessment of risks and environmental hazards associated with deployment.²⁴⁹

As part of the federal research effort, DOD, VA, and to a lesser extent, the Department of Health and Human Services (HHS) have funded hundreds of studies that relate to many of the identified research objectives. Each year, PGVCB and its successor interagency coordinating committees (Research Working Group of the Military and Veterans Health Coordinating Board and the Deployment Health Working Group) have catalogued federal research projects and described research findings related to Gulf War veterans' illnesses in annual reports to Congress.

Despite the long-established federal effort to identify research priorities, coordinate research, and fund specific studies, the priorities identified in the 1995 PGVCB report have yet to be satisfactorily addressed. For example, appropriate diagnostic tools and treatment methods for veterans' unexplained illnesses have not yet been identified, specific risk factors for these conditions have not yet been clearly determined or acknowledged by government agencies, and the prevalence of diagnosed and undiagnosed conditions, while chronicled in multiple studies, have yet to be firmly established or recognized by any federal agency. The Deployment Health Working Group's annual reports to Congress continue to identify multiple studies that relate in some way to the priority areas identified in its research plan. However, a demonstration of dollars spent or research that may relate to different aspects of Gulf War veterans' illnesses is not the same as a demonstration of progress made in identified priority areas.

Perhaps the most obvious shortfall in the federal research effort to date has been the ongoing emphasis on studies focusing on psychological stress as the principal factor in the development of Gulf War veterans' illnesses. As detailed in interagency committees' annual reports to Congress between 1994 and 2002, federal research efforts have included a large portfolio of studies focusing on deployment stress and psychiatric causes of Gulf War veterans' illnesses. As scientific evidence has cumulatively demonstrated a relatively minor role for psychological stress as a primary factor in the

etiology of Gulf War veterans' conditions, a shift in research focus has been needed to address the many other plausible explanations for veterans' illnesses. Unfortunately, as will be discussed in more detail, this shift has not yet taken place.

Gulf War-related research studies funded by the federal government. In its most recent annual report to Congress, published in April, 2004, the Deployment Health Working Group reported that federal agencies spent nearly 300 million dollars on Gulf War veterans' illnesses research through fiscal year (FY) 2002,⁷³ as shown in Table 13. As detailed in the report, direct federal costs for Gulf War illness-related research increased steadily after FY1994, reaching a peak level in FY2000. Thereafter, annual funding levels for Gulf War illnesses research declined steadily, and were projected to drop to just 19 million dollars in direct costs for FY2003, the lowest spending level since 1996.

Table 13. Projected Federal Funding for Gulf War Veterans' Illnesses Research through Fiscal Year 2003
(reported in millions of dollars)

Department	Actual Funding* FY1994 – FY2002	Projected Funding FY2003	Projected Total FY1994 – FY2003
DOD	219.1	13.5	232.6
VA	64.5	4.8	69.3
HHS	13.9	1.0	14.9
Total	297.5	19.3	316.8

* Total costs include both direct and indirect costs

Source: *Annual Report to Congress: Federally Sponsored Research on Gulf War Veterans' Illnesses for 2002*⁷³

Over the years, DOD has provided the bulk of federal research funding directed at Gulf War veterans' illnesses, and an extensive number of individual DOD-sponsored studies are chronicled in the 2002 Report to Congress. Of the DOD-sponsored projects identified as "Gulf War Research," the majority of studies specifically related to unexplained multisymptom illnesses and the effects of Gulf War-associated exposures were funded prior to FY2000. As previously described, those DOD-sponsored research projects have produced important breakthroughs in such areas as the chronic effects of low-level sarin exposure and neurological impairment in Gulf War veterans. However, DOD funding for this type of research has been dramatically reduced in the last several years, in keeping with DOD's shift from a focus on Gulf War veterans' illnesses to more general "deployment health" research. DOD's projected "Gulf War research" funding for FY2003 includes no new and just five

ongoing projects specifically related to Gulf War-related exposures and unexplained illnesses, and several projects related to prospective longitudinal assessment of post-Gulf War military personnel. Similarly, nearly all “Gulf War research” funding allocated by HHS since 2002 has been allocated for research on methods to improve the communication of health risks to personnel involved in post-Gulf War deployments.⁷³

As a result of DOD’s virtual withdrawal from the Gulf War-related health research effort, the Department of Veterans Affairs is the only federal agency currently sponsoring new research initiatives specifically targeting the unexplained health problems affecting Gulf War veterans. This change has had two major consequences. First, the overall amount of federal funding specifically focused on Gulf War-related research has declined considerably in recent years from an average of over 45 million dollars per year in direct and indirect costs between 1999 and 2001, to a projected total of just over 19 million dollars in direct costs in 2003. Second, the types of research undertaken and the scientists eligible to compete for available funding have dramatically changed. VA research funding is provided only to principal investigators employed as VA clinicians and scientists. Therefore, the range of research projects undertaken generally must fall within areas of expertise found “in house” at VA, with the exception of expertise provided by scientists outside of VA who collaborate in supporting roles with VA investigators.

As research relating to Gulf War veterans’ illnesses increasingly relies on VA support, it becomes ever more important that VA’s Gulf War research funding be well-focused and strategically allocated as part of a comprehensive plan designed to make significant progress on priority Gulf War illness research questions. However, it is clear from the research projects identified as comprising VA’s projected Gulf War Research portfolio for FY2003 that VA had not developed a strategic research plan aimed at addressing priority issues relating to the nature, causes, and treatments for Gulf War veterans’ illnesses. Of the nearly 4.8 million dollars projected by the Deployment Health Working Group to be allocated by VA in FY2003 for Gulf War Research, about 4.3 million was for research projects either initiated or continuing during FY2003.⁷³ Those projects are identified in Table 14, with an indication of whether the funded research focused on Gulf War-related undiagnosed illnesses or exposures, other Gulf War-related medical issues, or stress and psychiatric illness.

As shown, over 2.4 million dollars, or 57 percent, of VA’s FY2003 Gulf War research funding was projected to be allocated for projects related to stress and psychological illness. In contrast, only about 741 thousand dollars (17 percent) was to be allocated for projects directly related to understanding Gulf veterans’ undiagnosed conditions or the effects of Gulf War-related exposures. A similar amount was to be spent on projects unrelated to either Gulf veterans’ conditions or stress, such as a program to educate VA clinicians on bioterror events. Moreover, the few funded Gulf War illness-related projects, while valuable individually, appear to represent a somewhat haphazard collection of studies. None of the funded

Table 14. Projected VA Gulf War Research Expenditures for Fiscal Year 2003

	Focus of Research Project				Projected FY 2003 Expenditures (in dollars)
	Gulf War undiagnosed illnesses, effects of exposures	Other medical issues affecting Gulf War veterans	Stress and psychological illness	Other	
Spouses' and children's program		X			20,690
Follow-up of psychological Gulf War outcome: Relation to stress			X		72,700
Boston Environmental Hazards Research Center Program	X				297,000
San Antonio Environmental Hazards Research Center				X	300,000
Randomized clinical trial of cognitive- behavioral treatment for PTSD in women			X		1,386,700
ALS and veterans: Are veterans at increased risk?		X			139,600
Analysis of hippocampus volume in aging combat veterans with PTSD			X		135,000
HPA axis reactivity in men and women with chronic PTSD			X		101,300
Millenium cohort study				X	75,000
VHA clinicians and bioterror events				X	254,100
Neurochemical and neurobehavioral impact of pyridostigmine bromide treatment and stress	X				203,400
Stress, proinflammatory cytokines, and coping behavior			X		193,800
Pituitary adrenal function in people with fatiguing illness	X				135,000
Neuropsychological assessment of a population-based sample of Persian Gulf War veterans and controls	X				50,000
Neurobiology of severe psychological trauma in women			X		135,000
Associative learning in veterans with and without combat experience			X		74,000
A clinical trial of magnetic stimulation in depression			X		131,400
Improving outcomes of depression in primary care			X		201,926
Prospective assessment of neurocognition in future Gulf-deployed and Gulf-nondeployed military personnel	X				55,700
National registry of veterans with ALS		X			319,300
TOTAL FUNDING (\$)	741,100	479,590	2,431,826	629,100	4,281,616

Source: *Annual Report to Congress: Federally Sponsored Research on Gulf War Veterans' Illnesses for 2002*⁷³

projects addresses treatments for veterans' multisymptom illnesses, while the largest amount of projected funding for an individual study is provided for a behavioral therapy trial for PTSD. There is no evidence that VA has developed a comprehensive plan to fund studies of the highest priority and relevance to Gulf War veterans' illnesses, including those that follow up and capitalize on earlier breakthrough research findings. In fact, the Committee was puzzled to find that the scientific advances made in Gulf War-related research during 2002 were scarcely mentioned by the Deployment Health Working Group in its 2002 report to Congress.⁷³

Given the growing importance of VA's central role in sponsoring research on Gulf War veterans' illnesses, the Committee was extremely concerned that the projects identified to Congress as constituting VA's projected research program on Gulf War veterans' illnesses for 2003 still focused overwhelmingly on stress-related conditions, with relatively little funding specifically targeted for research related to veterans' multisymptom illnesses and the effects of Gulf War-related exposures. In light of the Committee's previous conclusions regarding the nature and potential causes of Gulf War illnesses, the FY2003 research portfolio outlined in Table 14 makes little sense, and provides a strong indication of why VA has made little progress in addressing Gulf War veterans' illnesses.

In October, 2002, VA announced that it would allocate up to 20 million dollars in FY2004 research funding for Gulf War veterans' illnesses and other deployment health-related projects, and issued a broad announcement describing the types of research projects that would be supported under this new initiative.³²⁸ In February, 2004, nearly halfway through the fiscal year that was to have included this expanded research effort, the Committee learned that VA had funded only one Gulf War illness-related study in FY2004, for less than 500 thousand dollars.

The lack of success in identifying and funding promising studies was disappointing in light of VA's FY2004 commitment, which had initially promised a fresh approach to research on Gulf War veterans' illnesses. VA's Office of Research and Development indicated to the Committee that Gulf War illness-related research proposals were not provided priority consideration under the deployment health initiative and were reviewed with other proposals by scientific panels that were not generally familiar with the issues and priorities associated with Gulf War illness-related research. Further, the funding commitment of "up to 20 million dollars" did not result in 20 million dollars being specifically set aside for deployment health or Gulf War illness research. In response to expressed concerns regarding the lack of progress made in association with the FY2004 funding initiative, VA has indicated to the Committee that it will redirect its research effort toward a more strategically designed and relevant Gulf War veterans' illnesses research portfolio. The Committee welcomes this renewed commitment by VA and the expressed willingness of VA's Office of Research and Development to utilize the Committee's recommendations in this work. The Committee looks forward to reviewing

tangible evidence of a comprehensive and more appropriately directed research program that addresses priority research areas and implements specific management provisions to ensure that identified objectives are addressed.

Overall, the Committee finds that, although a number of federally sponsored research studies have provided important scientific advances related to Gulf War veterans' illnesses, the federal research effort has yet to make the type of progress needed to improve the health of ill veterans. A large number of studies have been funded and a considerable amount of money spent, but federal agencies tasked with working together on Gulf War veterans' illnesses have not succeeded in developing research programs that comprehensively and successfully address priority research objectives. The recent reduction of federal research funding to address Gulf War veterans' illnesses is of particular concern now, as important advances relating to the nature of veterans' illnesses and possible long-term effects of Gulf War-related exposures are beginning to emerge from previously funded federal research. Such advances should be aggressively pursued, since research investments now have the greatest potential to reduce the suffering of ill Gulf War veterans as well as future costs associated with their medical care.

Finding 10 Recommendations

Overall progress in addressing Gulf War veterans' illnesses has been delayed by the lack of a well-coordinated federal research effort managed to successfully address key research priorities, and by an ongoing emphasis on studies that focus on psychological stress as the primary explanation for these conditions. The Department of Defense no longer supports new research on Gulf War veterans' illnesses, resulting in a dramatic decrease in federal funding in this area in recent years. This is of particular concern now, as recent breakthroughs provide new progress in understanding veterans' illnesses. The Committee therefore recommends that VA:

- Develop a comprehensive federal research plan to address Gulf War veterans' illnesses in conjunction with other participants in the Research Subcommittee of the Deployment Health Working Group and with the Research Advisory Committee on Gulf War Veterans' Illnesses. The plan should address priority research topics identified in this and future Committee reports. It should also utilize scientific resources and funding mechanisms available at each federal agency in order to enlist government and non-government scientific experts most capable of undertaking research projects that best address priority topics.
- In the context of the comprehensive federal research plan, adopt a strategic VA research program that identifies and addresses key research questions regarding the nature, causes, and treatments for Gulf War veterans' illnesses, utilizing research solicitations that address specific priority Gulf War illnesses research topics.

- Maintain a substantial research funding commitment to address the health consequences of Gulf War deployment until specific treatments and causes for these conditions are identified. Specifically, VA should allocate not less than 15 million dollars in each of the next four years in support of a comprehensive and well-managed research portfolio.
- Work with leading scientists—both those within VA and those not affiliated with VA—to develop comprehensive research protocols most capable of addressing priority Gulf War illnesses research questions.
- Establish an effective management strategy for the VA Gulf War illnesses research portfolio to ensure that studies capable of addressing priority research questions are satisfactorily developed and completed. The program should be directed by a doctoral-level scientist with appropriate expertise in research directly relevant to Gulf War veterans' illnesses.
- Adopt a mechanism for reviewing and funding Gulf War illnesses research proposals that takes into account the relevance of proposed projects to identified Gulf War illnesses research priorities, in addition to the scientific merit of the proposed research. Merit review panels should include scientists familiar with current research on Gulf War veterans' illnesses and established research priorities.
- Allocate a significant proportion of Gulf War illnesses research funding to treatment research, including specific annual allocations for the recommended treatment development program and pilot studies, and additional funding for small and large clinical trials, as scientifically appropriate.
- Give funding priority to studies that pursue significant research breakthroughs, such as those identified throughout this report. Do *not* fund studies in areas that accumulated research has found not to be useful in understanding the unexplained illnesses affecting Gulf War veterans, unless such proposals can be justified by new evidence or innovative hypotheses. For example, although psychiatric conditions such as posttraumatic stress disorder are appropriate topics for deployment health research in general, research proposals on Gulf War veterans' illnesses should not be funded if their principal focus is on psychological stress as the primary cause of these conditions.
- In conjunction with the Committee, regularly review progress on the objectives established for the Gulf War illnesses research program, to determine which have been adequately addressed, which should be revised, and which require additional follow-through with new and/or more specific funding announcements.

The Committee recommends that Congress:

- Set a national goal to develop treatments for the chronic multi-symptom illnesses affecting Gulf War veterans within five years.
- Establish line-item funding within the appropriations budgets of the appropriate federal departments that provides a total annual federal Gulf War illnesses research commitment adequate to execute the comprehensive Gulf War illnesses research plan, and in no event less than 45 million dollars, consistent with the annual funding levels invested in Gulf War illnesses research between 1999 and 2001.
- Designate that 15 million dollars of the annual federal Gulf War illnesses research funding be specifically added to VA's current research and development budget in support of the recommended comprehensive Gulf War illnesses research program. The balance should be provided to the Departments of Defense and Health and Human Services, as appropriate for the specific projects to be funded and, in particular, for research conducted by non-government research scientists on a competitive basis.

Conclusions

Recent scientific progress in understanding Gulf War veterans' illnesses has given new hope to ill veterans and provided a foundation for the important work that remains. These conditions have posed a difficult challenge for those whose health and lives have been affected by chronic and often debilitating symptoms for over a decade. Accumulated research evidence from studies conducted since the war clearly indicates that psychiatric illness and the effects of wartime stress cannot adequately explain Gulf War illnesses. In recent years, research studies have provided consistent evidence of linkages between exposure to neurotoxins during the war, particularly acetylcholinesterase-inhibiting compounds, and Gulf War veterans' illnesses. Numerous animal studies have demonstrated both that low-dose exposure to chemical nerve agents can produce chronic adverse neurological and immunological effects and that combinations of Gulf War-related exposures often work synergistically to yield toxic effects that exceed those resulting from individual exposures. These studies parallel clinical research findings demonstrating neurological injury and impairment in Gulf War veterans and epidemiologic studies that have consistently identified significant associations between veteran-reported neurotoxin exposures and higher rates of multisymptom illnesses. Other Gulf War-related exposures also may be linked to veterans' illnesses and will be more thoroughly addressed in future Committee reports.

While recent scientific advances in Gulf War illness-related research are encouraging, the most important work in effectively addressing these conditions lies ahead. The Committee judges research on Gulf War veterans' illnesses according to one standard: the extent to which it can contribute to improvements in the health of ill veterans. Federal research efforts thus far have not identified treatments that provide marked improvement for a substantial number of ill veterans, and no efforts have been undertaken to systematically identify and develop treatments that may hold promise. The Committee considers the identification of treatments to be the highest priority for Gulf War illness research and strongly urges VA to aggressively pursue this objective.

A number of other key research initiatives regarding the health of Gulf War veterans also require immediate action. Additional work is needed to identify the precise physiological mechanisms underlying veterans' multisymptom illnesses and the long-term effects of Gulf War-related exposures. The excess rate of amyotrophic lateral sclerosis among Gulf War veterans is particularly troubling and highlights the importance of determining whether Gulf War veterans are affected by excess rates of other neurological diseases such as Parkinson's Disease and multiple sclerosis. It is imperative that VA undertakes well-designed studies to evaluate rates of illness and death due to these conditions and establish an ongoing program to monitor the health of Gulf War veterans over time, utilizing existing databases to identify other conditions of possible concern. This should include regular reports of mortality rates, including deaths due to specific conditions, among Gulf War veterans in comparison to nondeployed Gulf War era veterans. Gulf War veterans have been particularly concerned about possible effects of their wartime service on

the health of their families, but clear information has not been available concerning the many unanswered questions in this area. Recent studies have suggested that children born to Gulf War veterans since the war may have higher-than-expected rates of some types of birth defects, although serious problems still appear, overall, to be rare. Systematic research is also needed to determine whether other family members of Gulf War veterans are affected by excess rates of illness, since no research findings in this area have yet been reported, including those from a large VA study of Gulf War era veterans' family members.

Overall progress in addressing key questions about Gulf War veterans' illnesses has been significantly delayed by the lack of a federal research strategy that effectively identifies key objectives and ensures that specific studies capable of satisfactorily meeting those objectives are carried out. Government-sponsored research on Gulf War veterans' illnesses has historically focused disproportionately on stress as an explanation for these conditions. This emphasis has continued in VA's Gulf War research portfolio to the present time, despite the lack of any indication that additional research in this area is likely to provide useful insights regarding the nature of or treatments for the multisymptom conditions affecting the majority of ill veterans.

In recent years, DOD has shifted its research emphasis and funding away from studies on Gulf War veterans' illnesses. As a result, overall federal funding for this research has declined dramatically, and VA is currently the only federal agency funding new studies on these conditions. The reduced Gulf War illnesses research effort is of particular concern now, just as significant breakthroughs are pointing the way toward new research capable of making significant progress. Reducing the federal commitment to research on Gulf War veterans' illnesses also makes little sense in light of its immediate relevance to current military deployments and domestic chemical defense.

The Committee applauds the important contributions of federally sponsored research studies that have provided important advances in understanding Gulf War veterans' illnesses. However, the federal research effort has not succeeded, overall, in answering important questions regarding the specific physiological mechanisms, contributing causes, and treatments for these conditions and has consequently not made significant progress toward improving the health of ill Gulf War veterans. It is imperative that VA and other federal agencies not lose sight of this central goal, nor of their continued responsibility to address the health consequences of service in the Gulf War.

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Appendices

Appendix A
Members of the
Research Advisory
Committee on Gulf
War Veterans'
Illnesses

James H. Binns (Committee Chair)

Mr. Binns is former Principal Deputy Assistant Secretary of Defense for International Security Policy, and a Vietnam veteran. He is also former chairman of Parallel Design and past president of A.D.R. Ultrasound, two medical imaging manufacturing companies which he led from startup to merger with major corporations. He is a graduate of Stanford University and Harvard Law School.

Nicola Cherry, M.D., Ph.D.

Dr. Cherry is Chair of the Department of Public Health Sciences at the University of Alberta. She is an occupational physician and epidemiologist with a particular interest in the effect of environmental chemicals on the nervous and reproductive systems. She was principal investigator on the U.K. study of Gulf War veterans conducted at the University of Manchester.

Beatrice A. Golomb, M.D., Ph.D.

Dr. Golomb is Assistant Professor of Medicine and of Family and Preventive Medicine at the University of California at San Diego, Research Associate Professor of Psychology at the University of Southern California, and a Robert Wood Johnson Generalist Physician Faculty Scholar. Her research focuses on the risks and benefits of medical interventions, especially cholesterol drugs, and on Gulf War veterans' illnesses. As a RAND scientist she traveled to the Middle East on a fact finding mission related to this issue, and has authored several RAND reports on the relation of exposures to illness in Gulf War veterans.

Joel C. Graves

Mr. Graves was enlisted for nine years and an armor officer for nine years. He is a Persian Gulf War veteran, and retired from the U.S. Army in 1997 as a captain. During the war, he was a member of the 1st Battalion, 67th Armored Battalion, 1st "Tiger" Brigade Independent Task Force, which took the northern part of Kuwait City. He has Gulf War syndrome.

Robert W. Haley, M.D.

Dr. Haley is Professor and Chief of the Epidemiology Division in the Department of Internal Medicine at the University of Texas Southwestern Medical Center in Dallas, where he holds the U.S. Armed Forces Veterans Distinguished Chair for Medical Research, Honoring America's Gulf War Veterans. Dr. Haley performed epidemiologic research at the U.S. Centers for Disease Control and Prevention from 1973-1983 before joining the medical school faculty in Dallas. His research includes national studies of hospital-acquired infections and other infectious diseases as well as studies on the neurophysiologic basis of Gulf War syndrome. He received the Commendation Medal of the U.S. Public Health Service for his research and is a member of the Association of American Physicians.

Marguerite L. Knox, M.N., N.P.

Ms. Knox served with the 251st Evacuation Hospital at King Khalid Military City, Saudi Arabia, during Desert Shield/Desert Storm. During her tenure as a Clinical Assistant Professor at the University of South Carolina College of Nursing, she was appointed by President Clinton to serve on the Presidential Advisory Committee on Gulf War Veterans' Illnesses from 1995-1998. Currently, LTC Knox serves as the 91W Healthcare Specialist Coordinator within the Medical Command of the South Carolina Army National Guard and works as Senior Sales Representative in the Neuroscience Division of Eli Lilly and Company.

William J. Meggs, M.D., Ph.D.

Dr. Meggs is Professor and Chief of the Division of Toxicology, Department of Emergency Medicine at the Brody School of Medicine at East Carolina University, where he also serves as Senior Vice Chair for Academic Affairs. His research interests include the role of neurogenic inflammation in chemical sensitivity, and the effects of low-level exposures to organophosphorous compounds. Dr. Meggs is a fellow of the American College of Medical Toxicology and the American College of Emergency Medicine, and served on the National Academy of Science's subcommittee on immunotoxicology.

Pierre J. Pellier, M.D.

Dr. Pellier is Vice President for the Clinical Department of the Neurosciences Medicine Development Centre, GlaxoSmithKline Pharmaceuticals, where he oversees the development of new drugs for neurological and psychiatric diseases. He holds a Doctorate of Medicine and a Specialist Diploma in hepato-gastroenterology from the Paris Medical Universities.

Stephen L. Robinson

Mr. Robinson is a former Airborne Ranger and Ranger instructor. His last assignment in the military was in the Office of the Secretary of Defense, working in the Preliminary Analysis Directorate for the Special Assistant on Gulf War Illnesses. Mr. Robinson has been the Executive Director of the National Gulf War Resource Center since 2001. He is a Gulf War veteran and a recognized expert on Gulf War illnesses and chemical and biological weapons exposures.

Steve Smithson

Mr. Smithson is an assistant director for the American Legion, with responsibility for Gulf War and deployment-related issues. He served on active duty in the United States Marine Corps from 1988-92, including a seven-month tour of duty in Saudi Arabia and Kuwait during the Gulf War.

Lea Steele, Ph.D. (Scientific Director)

Dr. Steele is Research Associate Professor in the College of Human Ecology at Kansas State University. She is an epidemiologist and human ecologist with a special research interest in the study of complex medical conditions that are difficult to diagnose and treat. Dr. Steele directed the Kansas Persian Gulf War Veterans Health Initiative, a state-sponsored research and service program, and was principal investigator of the Kansas Gulf Veterans Health Study.

Consultant to the Committee

Jack Melling, Ph.D.

Dr. Melling is former Chief Executive of the U.K. Microbiological Research Authority and was previously Director of the Salk Institute of Biologicals Development Center and Director of the Karl Landsteiner Institute for Vaccine Development. He is currently a consultant to the United States Government Accountability Office and a Senior Program Manager at the Battelle Memorial Institute.

Appendix B
2002-2004
Members of the
Expert Advisory
Panel for the
Research Advisory
Committee on Gulf
War Veterans'
Illnesses

Ira B. Black, M.D.

Chair, Department of Neurosciences and Cell Biology
University of Medicine and Dentistry-Robert Wood Johnson Medical
School

Floyd E. Bloom, M.D.

Chair, Department of Neuropharmacology
TSRI Scripps Research Institute

Joseph T. Coyle, M.D.

Eben S. Draper Professor of Psychiatry and Neuroscience
Harvard Medical School

Eugene Johnson, M.D.

Professor, Department of Neurology
Washington University

Marcel Mesulam, M.D.

Director, The Cognitive Neurology and Alzheimer's Disease Center
Northwestern University Medical School

James J. Tuite III

President, enviroSec, Inc.

Bailus Walker, Jr., M.D.

Professor of Environmental and Occupational Medicine
Howard University College of Medicine

Appendix C
Charter of the
Research Advisory
Committee on Gulf
War Veterans'
Illnesses

DEPARTMENT OF VETERANS AFFAIRS
CHARTER OF THE RESEARCH ADVISORY
COMMITTEE ON GULF WAR VETERANS' ILLNESSES

A. OFFICIAL DESIGNATION: Research Advisory Committee on Gulf War Veterans' Illnesses (RACGWVI).

B. OBJECTIVES AND SCOPE OF ACTIVITY: The Department of Veterans Affairs (VA) Research Advisory Committee on Gulf War Veterans' Illnesses shall provide advice and make recommendations to the Secretary of Veterans Affairs on proposed research studies, research plans, and research strategies relating to the health consequences of military service in the Southwest Asia theater of operations during the Persian Gulf War. The Committee shall not conduct scientific research.

The guiding principle for the work of the Committee shall be the premise that the fundamental goal of Gulf War-related government research, either basic or applied, is to ultimately improve the health of ill Gulf War veterans, and that the choice and success of research efforts shall be judged accordingly. The Committee shall assess the overall effectiveness of government research to answer central questions on the nature, causes, and treatments of Gulf War-associated illnesses.

The Committee shall review all relevant research, investigations, and processes for funding research conducted previously and assess their methods, results, and implications. The Committee shall review all proposed federal research plans, initiatives, procurements, grant programs, and other activities in support of research projects on Gulf War-associated illnesses. The Committee, consistent with law, shall have access to all VA documents and other sources of information it finds relevant to such review.

C. PERIOD OF TIME NECESSARY FOR THE COMMITTEE TO CARRY OUT ITS PURPOSE(S): The Committee was established in compliance with statutory instructions contained in Section 104 of Public Law 105-368. It has no termination date.

D. OFFICIAL TO WHOM THE COMMITTEE REPORTS: The Committee shall report to the Secretary of Veterans Affairs.

E. OFFICE RESPONSIBLE FOR PROVIDING THE NECESSARY SUPPORT TO THE COMMITTEE: The Department of Veterans Affairs will provide support for the Committee. A VA employee selected by the Secretary of Veterans Affairs shall be the Designated Federal Officer, under the direction of the Committee chair. Technical support for the Committee shall be provided by a staff that reports to the Committee chair, who may appoint a technical director for the staff to supervise its operation. Staff members may be VA employees, employees of other government agencies, or independent agents employed as temporary VA employees.

DUTIES FOR WHICH THE COMMITTEE IS RESPONSIBLE: The Committee shall provide to the Secretary of Veterans Affairs, not later than December 1 of each year, an annual report summarizing its activities for the preceding year. The Committee is authorized to develop additional reports and recommendations regarding relevant research. During its review of such research and in compliance with governing law, the Committee shall have access to all VA documents and other information sources it finds relevant to such review. Recommendations contained within a formal Committee report shall be submitted to the Secretary and other appropriate officials, as directed by the Secretary.

To augment the expertise of the Committee, the Secretary may authorize the Committee to contract for the services of non-governmental consultants who may prepare reports and background papers or prepare other materials for consideration by the Committee, as appropriate.

The Committee shall be comprised of members of the general public, including Persian Gulf War veterans, representatives of such veterans, and members of the medical and scientific communities representing appropriate disciplines such as, but not limited to, biomedicine, epidemiology, immunology, environmental health, neurology, and toxicology. The Secretary of Veterans Affairs may appoint non-US citizens as Committee members.

Members shall be appointed for two- or three-year terms. The Secretary may renew the terms of members. The Secretary shall appoint the chair of the Committee. The term of office for the chair shall be two years, also renewable by the Secretary.

The Committee may establish subcommittees to carry out specific projects or assignments. The Committee chair shall notify the Secretary upon the establishment of any subcommittee, including its function, members and estimated duration.

The Secretary may establish a panel of experts representing appropriate medical and scientific disciplines to assist the Committee in its work. Panelists may be called on by the Secretary for advice and consultation, and may advise the Committee on research or conduct other appropriate activities for the Committee, at the request of the Committee chair. Panelists shall report directly to the chair or such Committee members designated by the chair, but they shall not be members of the Committee. Panelists will be nominated by the Committee chair and appointed by the Secretary.

ESTIMATED ANNUAL OPERATING COSTS IN DOLLARS AND STAFF-YEARS: The estimated annual cost for operating the Committee and its support staff is \$400,000 and 4 FTE. All members will receive travel expenses and a per diem allowance in accordance with the Federal Travel Regulations for any travel made in connection with their duties as members of the Committee.

ESTIMATED NUMBER AND FREQUENCY OF MEETINGS: Meetings of the Committee shall occur not less than twice annually at the call of the chair. Meetings of the subcommittee(s) shall be convened as necessary. A federal government official shall be present at all meetings.

COMMITTEE TERMINATION DATE: None.

DATE CHARTER IS FILED:

	-- Signed --	4/19/04
APPROVED:	_____	_____
	Secretary of Veterans Affairs	Date

Abbreviations	ABT	Antibiotic Treatment Trial
	ACh	Acetylcholine
	AChE	Acetylcholinesterase
	AChEi	Acetylcholinesterase inhibitor
	ALS	Amyotrophic lateral sclerosis
	AVA	Anthrax vaccine adsorbed
	BChE	Butyrylcholinesterase
	CCEP	Comprehensive Clinical Evaluation Program
	CDC	U.S. Centers for Disease Control and Prevention
	CFS	Chronic fatigue syndrome
	ChE	Cholinesterase
	CI	Confidence interval
	CMI	Chronic multisymptom illness
	DEET	N,N-diethyl-meta-toluamide <i>or</i> N,N-diethyl-3-methylbenamide (an insect repellent)
	DFP	Diisopropylfluorophosphate, used to simulate nerve agents in laboratory research
	DOD	U.S. Department of Defense
	EBT	Exercise/Behavioral Therapy Trial
	EEG	Electroencephalogram
	FY	Fiscal year
	GAO	U.S. General Accounting Office, renamed the U.S. Government Accountability Office in July, 2004
	GWVIS	Gulf War Veterans Information System
	HHS	U.S. Department of Health and Human Services
	ICD-9	International Classification of Diseases, 9 th Revision
	IOM	Institute of Medicine
	MEG	Magnetoencephalography
	MRI	Magnetic resonance imaging
	MRS	Magnetic resonance spectroscopy
	MS	Multiple sclerosis
	NAA/Cr	N-acetyl-aspartate/creatine ratio
	NIH	National Institutes of Health
	NK	Natural killer cells
	NTE	Neuropathy target esterase

Abbreviations

OP	Organophosphate
PB	Pyridostigmine bromide
PET	Positron-emission tomography
PGVCB	Persian Gulf Veterans Coordinating Board
PON1	Paraoxonase
PTSD	Posttraumatic stress disorder
SF-36	Medical Outcomes Study Survey Form 36
SPECT	Single photon emission tomography
SSA	U.S. Social Security Administration
VA	U.S. Department of Veterans Affairs
VAMC	VA Medical Center
VBA	Veterans Benefits Administration, U.S. Department of Veterans Affairs
VHA	Veterans Health Administration, U.S. Department of Veterans Affairs
WRIISC	War-Related Injury and Illness Study Center