June 25, 2002

Hon. Anthony J. Principi
Secretary of Veterans Affairs
Department of Veterans Affairs
810 Vermont Avenue, NW, Suite 1000
Washington, D.C. 20420

Dear Mr. Secretary,

On behalf of the Research Advisory Committee on Gulf War Veterans Illnesses, I am pleased to submit this interim report. This report focuses on fundamental findings appropriate to this initial stage of our work. We look forward to making more detailed recommendations later this year. Based on our review of federal government and other research done to date, we have reached the following conclusions and recommendations.

Respectfully submitted,

James H. Binns, Jr.
Chairman
Research Advisory Committee on Gulf War Veterans Illnesses

Research Advisory Committee on Gulf War Veterans Illnesses
Interim Report
June 25, 2002

A. Conclusions

1. Gulf War veterans are ill. (See Appendix A.)

   a. They suffer from a pattern of health problems that significantly exceeds those seen in comparable populations, beyond that which is explained by stress or psychiatric diagnoses.

   b. Different epidemiological studies consistently show 25-30% of the veterans who served in the Gulf are ill, over and above the control population chosen for each study.

2. It is increasingly evident that at least one important category of illness in Gulf War veterans is neurological in character, according to recent scientific studies. (See Appendix B.) While these studies are not conclusive, there is enough evidence at present to conclude that this line of inquiry represents a potential breakthrough that should be aggressively pursued.

   a. Magnetic resonance spectroscopy suggests a loss of neurons in selected brain areas in ill veterans, particularly in the basal ganglia and brainstem. The areas of neuronal deficiency relate to veterans' symptoms. Veterans with cognitive problems show neuronal loss in the basal ganglia; those with muscle and joint problems show loss in the brainstem.

   b. Heart rate measurements show dysregulation of the autonomic nervous system in ill veterans

   c. Gulf War veterans are suffering from ALS at approximately twice the expected rate.

   d. A substantial increase in the cold sensory threshold has been measured in ill Gulf War veterans.

   e. Audiovestibular tests show abnormalities of central vestibular function.

   f. Ill veterans show elevated brain dopamine production.

   g. Ill veterans have low levels of an enzyme, paraoxonase, that is involved in breaking down organophosphates, and are more likely to have genotypes poor at metabolizing certain organophosphates, suggesting biochemical and genetic explanations for why some veterans became ill and others in the same location did not.

3. Many risk factors associated with Gulf War Illnesses are present today in Southwest Asia.

   a. Risk factors include exposures to environmental toxins, low-level nerve agents, depleted uranium, oil fires, mustard gas, stress, medical countermeasures to biowarfare and nerve agents, infectious diseases, and combinations of these factors.

   b. Several risk factors are also germane to domestic terrorism preparedness. Nerve agent exposure is a terrorist concern; and medical countermeasures for chem-bio warfare are relevant to homeland as well as military defense.

   c. Research on Gulf War Illnesses has broad implications to the war on terrorism.

B. Recommendations

1. Use all available methods to identify and evaluate treatments that may hold promise for the unexplained illnesses experienced by Gulf War veterans. Methods for evaluating potentially promising treatments should include, but not be limited to:

   a. Establish a program to monitor clinical outcomes associated with treatments recommended by current practice guidelines and/or commonly used by VA physicians to treat Gulf War veterans with unexplained illnesses;

   b. Establish pilot projects to evaluate existing claims regarding the effectiveness of treatments identified as effective for Gulf War illnesses;

   c. Solicit and investigate claims of treatment efficacy from clinicians and veterans;

   d. Collect data regarding specific treatments and lifestyle habits in existing and future projects that follow Gulf War veterans over time, and evaluate their associations with changes in veterans' health status.

2. Enlist the expertise of specialists in neurobiology and neurological illness in the national research effort on Gulf War Illnesses.

   a. This effort should include both individual experts from academia and the private sector as well as government agencies with relevant expertise like the National Institute of Neurological Diseases and Stroke and the Environmental Protection Agency.

   b. In addition to seeking advice, the research effort should seek the participation of these individuals and agencies in promoting and funding high quality Gulf War Illnesses research.

3. Designate as a research priority the investigation of neurological mechanisms, including acetylcholine dysregulation and other acetylcholinesterase inhibitor-induced

pathology, that potentially explain the disease process (in an important subset of ill veterans) and may lead to the development of treatments. (See Appendix C.)

a. Immediately solicit and fund research proposals on this priority topic.

4. Establish a research program to identify objective markers in ill veterans or subsets of ill veterans, and to investigate linkages between markers, exposures, and health status. Such studies are capable of identifying distinct illness syndromes, with specific causes, natural histories, diagnostic approaches, and responses to treatments. Objective markers include those that can provide information on character of exposures, on character of illness, and on mechanisms of illness.

5. Make full use of existing data on veterans' health and treatments.

   a. Merge Department of Defense databases on veterans' locations and exposures with the Veterans Benefits Administration database on veterans' health claims and diagnoses; and with the Department of Defense's Comprehensive Clinical Evaluation Program database, the VA Gulf War Registry database, and data from the VA National Survey of Persian Gulf Veterans. Consider including relevant databases from other sources, such as the Social Security Administration's National Death Index and Social Security Verification.

6. Manage for results.

   a. Solving a complex medical research problem requires sound scientific management of the overall program as much as well-executed individual studies. It is not surprising that the existing management structure has not produced the desired results. After reviewing Gulf War illness and related research programs in 1999, the Institute of Medicine of the National Academy of Sciences concluded that while "[m]any excellent efforts have been fielded . . ., [t]hese research efforts have in large part, however, not been undertaken in response to a well-developed and coordinated research agenda."

   b. Create a single business plan to drive the research program, identifying objectives and milestones, revised at least annually, and approved by the Secretary of Veterans Affairs and the Secretary of Defense.

   c. Open all research solicitations to open competition, allowing external as well as internal researchers to participate, as is presently done at the Department of Defense but not the Department of Veterans Affairs.

   d. Make peer review practices more open on the model of NIH peer review practices. To ensure customer orientation, place veterans on peer review panels after receiving peer review training.

   e. Place responsibility for the national research program in a central organization with the scientific expertise to manage it and the confidence and involvement of the

veteran community. In 1999 the Institute of Medicine recommended that responsibility for research into veterans' illnesses and deployment health be placed in an organization "independent of governance by any single federal agency in order to foster scientific excellence and assure scientific and public accountability." (See Appendix D.)

f. Pending the establishment of this national program, direct the Research Advisory Committee to review and advise on current and future research solicitations extended by the federal government related to Gulf War Illnesses, and all research proposals submitted.

7. Increase funding.

a. The opportunity to achieve a potential breakthrough in defeating Gulf War Illnesses through neuroscience research, the potential contribution to defeating other neurological diseases like ALS, and the need to protect current American forces and civilians as well as treat veterans, merit an increase in funding from current levels.

b. An adequate funding commitment is important to attract the best minds to the problem.

c. Funding research to develop treatments would not only alleviate suffering but would likely be more cost-effective than continuing care for chronic and possibly worsening conditions.

d. Provided management reforms are made to ensure funds are effectively spent, commit $150 million in federal funding for each of the next three years (compared to $350 million spent to date, according to the Department of Defense). Consider increasing this amount if initial results warrant.

APPENDIX A: SUMMARY OF EPIDEMIOLOGICAL EVIDENCE

The Symptoms, Prevalence, and Existence of Gulf War Veterans' Illnesses:
What Do We Know From Epidemiologic Research?

Prepared by Lea Steele, Ph.D.

Summary of Presentation to the Research Advisory Committee on Gulf War Veterans' Illnesses
U.S. Department of Veterans Affairs. April 11, 2002

The health problems reported by Gulf War veterans since the end of Desert Storm have posed a complex and often 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 typically the first scientific approach taken in understanding unexplained health problems. Since the Gulf War, 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.[1-11] Despite the diversity of research approaches and groups studied, a number of common threads have emerged from these investigations, providing preliminary answers to key questions about the characteristics, prevalence, and existence of veterans' unexplained illnesses, as well as evidence regarding their association with service in the Gulf War.

Gulf Veterans Experience High Rates of Symptoms and Diagnosed Conditions

Epidemiologic studies comparing mortality and hospitalization rates between Gulf War veterans and era veterans who did not serve in the Persian Gulf region (non-Gulf veterans) have, overall, found few differences with respect to disease-related deaths and hospitalization rates.[12-16] It will be important to follow Gulf veterans for years to come in order to monitor deaths due to diseases with longer latency periods, such as cancer. But at this time, the observed similarities between Gulf and non-Gulf veterans in terms of mortality and hospitalizations stand in contrast to findings regarding a group of poorly understood health problems not generally associated with hospitalization or death.

The most prominent and consistent findings to emerge from population-based studies of Gulf War-era veterans are that Gulf veterans experience a wide range of symptoms at significantly higher rates than non-Gulf veterans, and that Gulf veterans in different studies report similar constellations of symptoms. Representative symptoms reported by Gulf and non-Gulf veterans in a survey of over 20,000 U.S. Gulf War-era veterans are shown in Table 1.

Table 1. Proportion of U.S. Gulf War-era Veterans Reporting Symptoms in a National Survey[9]

	Gulf War veterans	*Non-Gulf veterans*
Headache	54%	37%
Joint pain	45%	27%
Fatigue	38%	15%
Difficulty concentrating	35%	13%
Diarrhea	31%	15%
Skin rash	29%	13%
Shortness of breath	24%	11%
Dizziness	22%	10%

Note that these symptoms, individually, are not unique to Gulf War veterans, in that they are also experienced by veterans in the non-Gulf veteran comparison group. This is not surprising, since it has long been known that some level of symptomatology is found in any population group.[17,18] But Gulf War veterans report these symptoms in patterns that are distinct from other veterans and from the general population,[19,20] that is, they experience multiple different types of symptoms simultaneously, over a long period of time. For example, while anyone might have occasional headaches or digestive problems or joint pain, 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. 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.[5,9,10]

In addition to undiagnosed symptoms, population-based studies have found that Gulf veterans report significantly higher rates of some types of diagnosed medical conditions than non-Gulf veterans. The Department of Veterans Affairs recently announced that Gulf veterans have been approximately twice as likely as non-Gulf veterans to develop a serious neurodegenerative disease, amyotrophic lateral sclerosis, in the years since the war.[21] In addition, studies have found that Gulf veterans report significantly higher rates of diagnosed respiratory conditions, migraines, skin conditions, gastrointestinal conditions, and some psychological conditions, than non-Gulf veterans.[9,10] However, Gulf veterans have not reported increases in most age-related chronic conditions such as cancer, heart disease, and diabetes.[9,10]

The 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 a substantial number of Gulf War veterans are ill. However, reports from government review panels and researchers have suggested that these conditions may not result from experiences or exposures specific to the Gulf War.[22-24] Is there evidence that veterans' unexplained health problems are linked to their wartime service?

Many epidemiologic studies have identified significant associations between illness and a variety of exposures which veterans report experiencing during the Gulf War, including smoke from oil well fires, receipt of multiple vaccinations, heavy use of pesticides, hearing chemical alarms, ingestion of pyridostigmine bromide, and pesticide use.[3,6,25-30] These findings have been considered to be inconclusive, however, due to limitations in veterans' knowledge and recollection of what they might have been exposed to, and at what levels.

Additional evidence linking veterans' illnesses to their service in the Gulf War is provided in a study of Kansas veterans which found illness rates to be significantly associated with the locations in which veterans served during the war.[10] Gulf War illness rates were lowest (21%) in Gulf veterans who served primarily on board ship during the war, 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 all coalition air strikes took place. Illness rates also varied with the time periods veterans were present in theater, with lowest rates (9%) among veterans who departed the region before the start of the air war in January, 1991, and a substantially higher rate (25%) among veterans present during Desert Storm who left the region in March of 1991, within a month of the cease-fire. But the highest rate of illness (43%) was found in veterans who didn't leave until 4-5 months after the cease-fire, regardless of the total length of time they spent in theater.

The nonrandom distribution of illness in Kansas veterans (identified prior to any media reports linking illness to time and place), and the unexpectedly high illness rates in veterans who were present in theater months after the cease-fire provide strong evidence that veterans' illnesses are associated with events and exposures specific to the Gulf War, evidence that is independent of veterans' recollections concerning specific exposures.

Is Stress the Cause of Gulf War Illnesses?

Early reports suggested that the unexplained illnesses reported by Gulf War veterans were due to wartime stress.[22,31] As additional research has become available, however, it has become evident that the unexplained health problems reported by Gulf veterans cannot be adequately explained by deployment stress, wartime trauma, or psychiatric diagnoses such as post-traumatic stress disorder (PTSD).[23] 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. Casualties were very low, and the vast majority of veterans were never in combat areas[9,10] and did not witness any deaths.[9,25]

Of course, some individuals did experience traumatic events during the Gulf War, and may now experience psychological problems as a result. Data from multiple sources, however, indicate that only a small fraction of veterans with health concerns since Desert Storm suffer from PTSD. The Department of Veterans Affairs has reported that PTSD accounts for less than 5% of the diagnoses made in veterans examined in their Gulf War registry.[32] Similarly, a RAND report commissioned by the Department of Defense to review the scientific evidence concerning stress and Gulf War illnesses[33] concluded that overall rates of PTSD are low in Gulf War veterans, and found little evidence linking stress to symptoms or physical disease (p.65).

Recent studies, using more sophisticated evaluation and analytic approaches, verify that Gulf veterans experience higher illness rates than non-Gulf veterans, even after controlling for the effects of wartime stressors and current psychiatric diagnoses.[27,34-36] A related observation comes from a large British study which found high rates of symptoms and symptom complexes in Gulf War veterans, but not in veterans who served in the Bosnian conflict, an indication that these conditions were the result of experiences specific to the Persian Gulf theater, and not a more generalized psychological reaction to the stress of deployment to war.[6]

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. Although government and media reports often say that about 100,000 U.S. Gulf veterans (14%) are affected by Gulf War-related health problems, this number is not based on any research study. Research 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 (Table 2).

But a surprisingly consistent estimate of the excess rate of illness in Gulf veterans has emerged from several studies, using different definitions of "multisymptom illness," as shown in the right column of Table 2. This is important, since the prevalence in non-Gulf veterans provides an estimate of the rate of illness expected in the absence of service in the Gulf War, and the "excess" rate in Gulf veterans provides an indicator of illness resulting from Gulf War service.

Table 2. Prevalence Estimates of Multisymptom Illness in Gulf and non-Gulf Veterans

Group Studied	***Case Definition Used***	***Prevalence in Gulf Veterans***	***Prevalence in Non-Gulf Veterans***	***Excess in Gulf vs. Non-Gulf Veterans***
PA Nat'l Guard[5]	CDC Multisymptom	45%	15%	30%
U.K. veterans[6]	CDC (modified)	62%	36%	26%
Kansas veterans[10]	KS Gulf War Illness	34%	8%	26%
Kansas veterans[10]	CDC Multisymtom	47%	20%	27%

Regardless of whether the symptom pattern is defined broadly (as in the study of U.K. veterans), or conservatively (as in the study of Kansas veterans), the level of illness experienced by Gulf veterans in excess of the level in non-Gulf veterans is consistently between 26-30%, suggesting that 26-30% of Gulf veterans are affected by a complex of multiple symptoms in connection with their Gulf War service.

Summary of Epidemiologic Findings: What Do We Know?

Although many questions remain about the nature and causes of health problems affecting Gulf War veterans, a number of key conclusions can be drawn from existing epidemiologic research.

- Gulf War veterans are ill. They experience significantly more symptoms, illnesses, and diagnosed conditions than veterans who did not serve in the Gulf War.
- Gulf War veterans' illnesses are associated with their experiences during the war.
- Elevated illness rates observed in Gulf veterans are not explained by wartime stress or psychiatric diagnoses.
- Between 25 and 30 percent of Gulf War veterans are affected by multisymptom illnesses associated with their wartime service.
- The unexplained health problems affecting Gulf War veterans have generally not been associated with increases in disease-related mortality or hospitalization rates.

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APPENDIX B: SUMMARY OF NEUROLOGICAL FINDINGS

Prepared by Robert Haley, MD

Summary of Presentation to the Research Advisory Committee on Gulf War Veterans' Illnesses
U.S. Department of Veterans Affairs. April 11, 2002

I. Early Findings Suggesting a Possible Neurologic Syndrome

Evidence of a Gulf War Syndrome

In 1997 Haley, Kurt and Hom reported three primary syndrome-like symptom complexes identified by exploratory factor analysis of typical symptoms of Gulf War syndrome in a battalion of U.S. Naval Reserve construction troops.[1] Haley syndrome 1 comprised distractibility, forgetfulness, depression, and daytime somnolence, etc. ("impaired cognition"); syndrome 2, more profound reduced intellectual processing, confusion, frequent disorientation and episodes of vertigo ("confusion-ataxia"); and syndrome 3, chronic somatic pain and paresthesias of the extremities ("central pain"). These syndromic constructs were replicated by confirmatory factor analysis in which a model of simultaneous structural equations from the first study was demonstrated to fit well the symptom data of an independent sample of 335 regular U.S. Army veterans of the Gulf War.[2]

In a survey of over 20,000 from random samples of the deployed and nondeployed Gulf War-era veteran populations, Kang et al. of the VA Central Office performed an exploratory factor analysis and identified three syndrome factors closely resembling the three Haley syndrome factors and concluded that syndrome factor 2, found only in the deployed population, represented a "unique Gulf War syndrome." This study was presented as a poster and published as an abstract at the 1999 Conference on Federally Sponsored Research on Gulf War Illness[3] but has not been published in a peer-reviewed journal.

Recently, Cherry et al. reported the results of a survey in a random sample of deployed and nondeployed British Gulf War-era veterans in which exploratory factor analysis obtained syndrome factors named "psychological," "neurological" and "peripheral," among others, which appeared similar to the three Haley syndromes.[4]

Other research groups attempted to apply exploratory factor analysis to previously collected survey data with mixed results. Fukuda et al. of CDC identified two factors resembling Haley factors 1 and 3 but had not measured the symptoms to identify factor 2.[5,6] The surveys of Knoke et al.[7,8] and Doebbeling et al.[9,10] measured symptoms of common psychiatric diseases rather than those of Gulf War syndrome and consequently derived factors reflecting these extraneous conditions. Ismail et al., studying British Gulf War veterans, measured symptom sets too different to evaluate the Haley syndrome factors.[11,12] The conflicting findings from the studies that measured mostly common psychiatric and atypical symptoms have prevented a consensus on whether a neurologically based syndrome exists.

Studies of functional status and neuropsychological measures have also suggested neurologic involvement but have not been compelling.

Functional Status Measures

In their 1997 report Haley, Kurt and Hom reported that Gulf War veterans meeting their case definition of syndrome 2 ("confusion-ataxia"), but not those with the other two syndromes, were far more likely to be unemployed than the well veterans in the battalion.[1]

In a large random sample survey of Gulf War veterans from Iowa, the Gulf War veteran population as a whole scored 3-7 points lower (on a 100-point scale) on all measures of the MOS SF-36 test of functional status than the non-deployed veteran population.[13] Although these differences were statistically significant, they greatly underestimated the extent of impairment by combining the relatively small percentage of deployed veterans who are ill with the much larger number of deployed veterans who remained well.[10]

Recently, Haley, Maddrey and Gershenfeld addressed this problem by administering the MOS SF-36 to groups of ill Gulf War veterans fitting the Haley syndromes versus controls and found substantial functional impairment (40-60 points lower than well veterans) comparable to common disabling diseases including congestive heart failure, recent myocardial infarction, diabetes, and emphysema.[14]

Neuropsychological Tests

A large body of studies in the Gulf War illness literature have involved psychological and neuropsychological tests.[for example,15-19,19,20] The preponderance of findings indicate subtle deficits on a variety of measures in ill veterans compared with either deployed or nondeployed controls. Subtle neurocognitive deficits tend to be correlated with psychological measures of depression and somatic complaints, a pattern found commonly in both major depressive disorders and in neurologic disorders, and the various research groups disagree on the implications of this broad array of subtle abnormalities. Consequently, the contribution of neuropsychological testing to understanding the problem has been limited.

II. Objective Markers of Neurological Disease

A growing body of research, particularly within the past two years, provides objective evidence of neurological disease in Gulf War veterans.

Neurophysiological Tests

Cold Sensory Threshold. As early as 1996 Jamal et al. reported the results of neurophysiologic tests, including quantitative sensory tests, sensory and motor nerve conduction studies, visual, somatosensory and brainstem auditory evoked potentials, and electromyography in a pilot study including 14 Gulf War veterans with fatigue, weakness, paresthesias, numbness, temperature disturbances, and somatic pain, and 13 well civilian controls.[21] They found a substantial increase in the cold sensory threshold (cases 0.55 C°, controls 0.25 C°, $p < 0.0002$) but no difference in warm or vibratory thresholds and only marginally significant differences on 2 of 12 nerve conduction parameters.

Haley et al. recently replicated Jamal's finding of an increased cold threshold and the absence of abnormalities on the other neuromuscular tests in their series of cases and controls (unpublished data).

Audiovestibular Tests. In their 1997 report Haley et al. presented the results of audiovestibular tests that would be sensitive to subtle damage to brainstem reflex pathways.[22,23] Compared with the 23 age-sex-education-matched controls, the veterans with Haley syndromes 2 were significantly more likely to have pathologic nystagmus and abnormal ocular motility, and

increased interocular asymmetry of saccadic velocity (eye reflexes), and to have significantly reduced saccadic velocity after caloric vestibular stimulation, increased intraocular asymmetry of gain on sinusoidal harmonic acceleration, and interside asymmetry of wave I-III latency on auditory brainstem evoked response. Syndromes 1 and 3 generally scored between the more nearly abnormal syndrome 2 patients and the controls. The investigators concluded that the findings were most compatible with a subtle abnormality of central vestibular function involving the vestibulo-ocular reflex mediated by neural pathways in the brainstem or basal ganglia.[23]

Autonomic Nervous System Function. Haley et al. recently completed a thorough evaluation of autonomic nervous system function, including 24-hour measurements of heart rate variability, blood pressure and body temperature, direct recording of sympathetic nerve activity in a peripheral nerve at rest and under orthostatic stress, tests of sudomotor function, sleep studies, etc., in 22 ill Gulf War veterans and 18 age-sex-education-matched control veterans from the same battalion. The report, presented at the 2000 Conference on Federally Sponsored Research on Gulf War Illness[24] and presently undergoing journal peer review, documents substantial blunting of the normal increase in high frequency heart rate variability during sleep, the most sensitive sign of early autonomic nervous system dysfunction. If accepted by journal peer review and more widely verified, this finding could explain common Gulf War symptoms such as the perception of poor sleep, morning fatigue, chronic pathogen-free diarrhea and the reported increase in cholecystitis and cholecystectomies in young male Gulf War veterans compared with other veterans.[25]

Neuroimaging Studies

Initial MR Spectroscopy Studies. In their initial 1997 nested case-control study, Haley et al. performed standard brain magnetic resonance imaging (MRI) and found no structural differences.[22] Noting the similarity of the symptoms of GW syndrome and the early presenting symptoms of primary diseases of basal ganglia, Huntington's, Wilson's and Fahr's diseases,[26] in a subsequent study they performed long echo time (TE=272) proton (^{1}H) magnetic resonance spectroscopy (MRS) of 4x2x2-cm single voxels in right and left basal ganglia (deep brain structures) and a 2x2x2-cm single voxel in the pons (brainstem).[27] The ratio of N-acetyl-aspartate to creatine (NAA/Cr), a non-specific measure of functional neuronal mass (brain cell health), was significantly lower in all three brain regions in the 22 ill Gulf War veterans than in the 18 age-sex-education-matched control veterans ($p = 0.007$). The NAA/Cr ratio was reduced in all three brain regions in the veterans with Haley syndrome 2 (for example, in the right basal ganglia, cases 3.60 ± 0.11, controls 4.08 ± 0.13, a 12% difference, $p = 0.003$). The NAA/Cr ratio was marginally reduced only in both basal ganglia but not in the pons in syndrome 1, and only in the pons but not in the basal ganglia in syndrome 3. The NAA/Cr ratio was also lower in all three brain regions of 6 additional ill veterans with Haley syndrome 2, recruited from a new survey U.S. Army veterans in North Texas as a replication sample. The investigators concluded that Gulf War veterans with different clinical syndromes have biochemical evidence of neuronal damage in different distributions in the basal ganglia and brainstem

Independent Replication. Following the initial report of the Haley et al. MRS finding at the 1999 Radiological Society of North America, Weiner and colleagues at the San Francisco VA Medical Center and UCSF Medical School undertook a study to test the finding in an independent group of veterans. In 11 ill Gulf War veterans fitting the definition of Haley syndrome 2 and 11 non-veteran controls, all without history of alcohol abuse, major depression or PTSD, the investigators performed a similar protocol of long echo time, proton MRS on the right basal ganglia, with additional methodologic refinements (e.g., MRI segmentation). The

results showed a similar reduction in the NAA/Cr ratio (cases 3.62 ± 0.41, controls 4.06 ± 0.72, p = 0.05), not confounded by partial-volume effects.[28]

Neurohormonal Studies

Simultaneous with the neuroimaging study, the Haley group hospitalized the 23 ill Gulf War veterans and 20 controls in the General Clinical Research Center (GCRC) of UT Southwestern Medical Center for 6 days in a low-stress environment with a standardized high-salt, low tyrosine diet. At the end of the period, a venous blood sample was drawn at exactly 7:30 AM after a 14-hour overnight fast, and assays were run for homovanillic acid (HVA) and 3-methoxy-4-hydroxyphenlyglycol (MHPG). In the syndrome 2 veterans versus the controls the HVA/MHPG ratio, an index of central nervous system dopamine production rate, was found to have a strong inverse association with the NAA/Cr ratio of the left basal ganglia ($R2 = 0.56$, $p < 0.0001$) but not with that of the right basal ganglia or the pons, following the laterality of dopamine effects in striatal ablation studies in rodents.[29] Specifically, veterans with more brain cell damage in the left basal ganglia (lower NAA/Cr ratio) had higher brain dopamine production, a finding compatible with upregulation of dopamine receptors after damage to dopaminergic pathways in the basal ganglia. The investigators concluded that the finding supports the theory that Gulf War syndrome is a neurologic illness, in part related to injury to dopaminergic neurons in the basal ganglia.

Genetic Predisposition

Initial Genetic Studies. In their initial 1997 epidemiologic report, Haley and Kurt reported that all three Haley syndromes were strongly associated with risk factors for exposure to cholinesterase-inhibiting organophosphate or carbamate chemicals: namely, syndrome 1 was associated with organophosphate pesticides in flea collars (relative risk, RR, 8.2, $p = 0.001$.) ; syndrome 2, with apparent low-level nerve agent exposure (RR 7.8, $p < 0.0001$) and with advanced side effects of pyridostigmine bromide anti-nerve agent prophylactic medication (RR 32, $p < 0.0001$); and syndrome 3, with high-concentration DEET insect repellant, $p < 0.0001$) and with advanced side effects of pyridostigmine (RR 3.9, $p < 0.0001$).[30] The unpublished survey by Kang et al. found virtually the same association of syndrome 2 with low-level nerve agent exposure (RR 6.9, $p < 0.0001$).[3] Cherry et al. found days handling pesticides to be strongly associated with their "neurological" factor and with symptoms consistent with toxic neuropathy.[31]

From these epidemiologic findings, Haley, Billecke and La Du reasoned that, if Gulf War syndromes had been caused by exposure to cholinesterase-inhibiting organophosphate and carbamate chemicals (e.g., chemical nerve agent, pesticides, and pyridostigmine), individuals born with lower blood levels of enzymes that inactivate these chemicals would have been more susceptible and thus would have been more likely to be injured by their exposures.[32] As part of the nested case-control study in the UT Southwestern GCRC, they obtained a venous blood sample for assay of plasma activity of butyrylcholinesterase (BChE) and the allozymes of paraoxonase/arylesterase, the two enzymes that inactivate organophosphates, and for genotypic determination for BChE variants and polymorphisms of the PON1 gene for paraoxonase/arylesterase (type Q vs type R). Compared with the 20 age-sex-education-matched control veterans, the 26 Gulf War veterans with Haley syndromes had much lower plasma levels of the type Q paraoxonase/arylesterase enzyme. The difference was greatest for Haley syndrome 2 and intermediate for syndromes 1 and 3, again reflecting the relative degrees of severity of the three syndromes. The cases and controls did not differ on the type R paraoxonase/arylesterase

allozyme, total paraoxonase or BChE levels. Veterans in the lowest quartile of type Q activity were 9 times more likely to have syndrome 2 than those with higher levels ($p = 0.009$). Genotype (having the R allele) was also predictive (odds ratio 3.3, $p = 0.05$). The allozyme-specificity of the finding was important because the type Q allozyme has high hydrolytic activity against the organophosphate nerve agents sarin and soman but low activity against common pesticides such as parathion and malathion; whereas, the type R allozyme has the converse. Blood levels of paraoxonase/arylesterase allozymes remain unchanged throughout life; whereas, BChE levels may be reduced by organophosphate or carbamate chemical exposures. The investigators concluded that the findings further support the proposal that neurologic symptoms in some Gulf War veterans were caused by environmental chemical exposures.

Replication Studies. The plasma samples from the Haley, Billecke, La Du study were transferred to the laboratory of C. A. Broomfield in the Biochemical Pharmacology Branch, U.S. Army Medical Research Institute of Chemical Defense, Aberdeen Proving Ground, Maryland, where they were tested for enzymatic activity against sarin and soman chemical nerve agents. The purposes of the experiment were to determine if the type Q paraoxonase/arylesterase activity measured in the prior study actually reflected hydrolytic activity against the presumed cause of the Haley syndromes and to attempt to replicate the test results in an independent laboratory. The results demonstrated that the hydrolytic activity against sarin and soman was significantly lower in the Haley syndrome patients than in the controls just as in the prior study.[32]

Mackness et al. recently published a report from a privately funded study demonstrating that the total paraoxonase blood level of 152 ill Gulf War veterans was less than 50% that of 152 civilian controls (100.3 vs 215, $p < 0.0001$) but that the genotype did not differ significantly between the groups.[33]

Related Studies. Cherry, Mackness et al. recently reported reduced paraoxonase and R allele predominance in British sheep dippers with fatigue-cognitive-pain syndromes similar to Gulf War syndrome and chronic fatigue syndrome.[34] Japanese researchers have cited the racial predominance of the PON R allele and low type Q allozyme levels in Asians as a possible explanation for the high attack rate of the low level sarin exposures in the 1995 Aum Shinrichyo terrorist attacks in the Tokyo and Matsumoto subways.[35] The R allele predominance in the PON1 genotype has also been found to be associated (odds ratio, 1.6) with the development of Parkinson's disease.[36]

III. Relationship Between Gulf War Syndrome and Neurodegenerative Diseases

The studies described above have raised questions of whether Gulf War veterans may be at higher risk of prematurely developing neurodegenerative diseases as a result of environmental exposures in the Gulf War.

Amyotrophic Lateral Sclerosis

VA researchers headed by Dr. Ronald Horner at Duke University and the Veterans Administration Hospital in Durham, North Carolina have completed an epidemiologic study of ALS demonstrating that Gulf War veterans were approximately twice as likely to contract ALS as Gulf War-era veterans who did not serve in the Gulf War. Although the report of these findings remains in journal peer review at present, the epidemiologic connection appears likely, and the Secretary of Veterans Affairs has approved service-connected benefits for Gulf War veterans with ALS. Exposure to organophosphates, a class of chemicals including pesticides and

nerve gas to which soldiers were exposed in the Gulf War, is one of the risk factors for ALS that has been identified in previous epidemiologic studies.[37,38]

Parkinson's Disease

At present there is no definite evidence that Parkinson's disease is occurring at increased rates or at unusually early ages in Gulf War veterans; however, emerging threads of evidence suggest that such could occur. Several researchers have observed anecdotal cases of tremors or movement impairment, usually in the hands, in atypically young Gulf War veterans, who say that the problems began during or just after the war (unpublished data). As noted above, symptoms of Gulf War syndrome resemble those of the early presenting symptoms of primary degenerative diseases of basal ganglia, a brain region that is also affected in Parkinson's disease.[26,27] The genetic profile (low blood PON1 paraoxonase enzyme concentration and R allele predominance) found to be a risk factor for Gulf War syndrome[32] has also been found to predispose to Parkinson's disease.[36] Brain dopamine production, which is an important abnormality leading to Parkinson's disease, has also been found to be abnormal in Gulf War syndrome.[29]

Implications for Preventing Neurodegenerative Diseases

The possibility of links between Gulf War syndrome and the later development of neurodegerative diseases like ALS and Parkinson's disease increases the urgency of research to clarify these issues. Confirmation of such links would suggest a need to develop ways of screening veterans for susceptibility or early signs so that preventive strategies could be tried. Possible preventive strategies might include avoidance of further organophosphate exposures and administration of neuroprotective medications.

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APPENDIX C: EVIDENCE LINKING ACETYLCHOLINESTERASE INHIBITORS, AND ACETYLCHOLINE DYSFUNCTION, TO ILLNESS IN GULF WAR VETERANS

Beatrice A. Golomb, MD, PhD

Acetylcholinesterase inhibitors appear to be causally linked to illness in ill Gulf War veterans.

Acetylcholine dysregulation is a mechanism that may explain the disease process in one major form of Gulf War illness, whatever the cause of the dysregulation. The following summary of work submitted for publication by Golomb demonstrates that acetylcholine dysregulation and associated pathology can be caused by exposure to acetylcholinesterase inhibitors present in the Gulf War experience. Work of Dr. Hermona Soreq and colleagues has suggested that both acetylcholinesterase inhibitors and certain stressful exposures are related to acetylcholine dysregulation and associated pathology[1, 2].

Acetylcholinesterase inhibitors are agents that block normal regulation of the nerve signaling chemical "acetylcholine", that is involved in regulation of muscle function, memory, sleep, pain, gastrointestinal function, skin function, and emotion. Acetylcholinesterase inhibitors include pyridostigmine bromide, a nerve agent pretreatment pill given to an estimated 250,000 Gulf War troops; organophosphate and carbamate pesticides, used to minimize insect-born illness; and organophosphate nerve agents, to which an estimated >100,000 troops were exposed following incidents such as the Khamisiyah ammunitions depot demolition.

Hill's criteria for causality are a set of criteria that are widely used to adjudicate the likelihood that an exposure is causally linked to an outcome. These criteria are applied in settings in which randomized trial data cannot be obtained. (In general, when it is thought that an exposure leads to harm, randomized trials cannot ethically be performed to evaluate that hypothesis.) Hill's criteria consists of 7 desiderata: the association (between the exposure and the outcome) should be strong; it should be consistent; the cause should precede the effect; there should be a biological gradient, or dose-response effect; the effect should be biologically plausible; there should be concordance with preexisting literature; and the effect should be, perhaps, specific (though the criterion of specificity is routinely violated, since many exposures cause more than one outcome).

Strong relations of acetylcholinesterase inhibitors to illness have been observed.

These relationships are consistent in that each class of cholinesterase inhibitor to which Gulf War veterans have been exposed appears to separately be linked to increased reporting of health symptoms.

The connection is temporally appropriate, in that exposure occurred prior to increased illness reporting.

A connection is biologically plausible, since

- Many distinct elements of acetylcholine regulation have been shown to be disrupted following exposure to acetylcholinesterase inhibitors, and some of these changes in regulation are long-lasting or permanent

- This might be expected to lead to dysfunction in the domains that acetylcholine is involved in regulating, namely cognition, muscle function, sleep, pain, skin function, and gastrointestinal function

- These are domains that figure prominently in complaints of ill Gulf War veterans.

The link is specific, in the sense that people given acetylcholinesterase inhibitors for treatment of medical conditions report side effects in domains that accord with domains of symptoms in ill Gulf War veterans, while persons with the same condition who are treated with unrelated agents report different classes of symptoms. Additionally, basic science research shows prominent regional localization of acetylcholinesterase inhibitor activity (and of certain types of acetylcholine receptors) to a brain region called the basal ganglia; while studies in ill Gulf War veterans suggest that regional alterations in brain activity may localize most prominently to the basal ganglia.

There is concordance with existing literature, in that similar findings of increased symptoms across many health domains have been reported in studies of persons exposed to acetylcholinesterase inhibitors through industrial and accidental exposures.

A particularly compelling line of inquiry, from the standpoint of causality, is evidence that ill veterans differ statistically from healthy veterans in both the prevalence of poor-metabolizing genetic variants of enzymes that break down certain acetylcholinesterase inhibitors; and in the activity level for such metabolizing enzymes. Because genetic and physiological differences in acetylcholinesterase inhibitor metabolizing enzymes are not subject to manipulation by subjects, concerns regarding self-report and recall bias are not germane (when health status is obtained without subject knowledge of their biochemical state); these findings are particularly difficult to explain through other than a causal mechanism.

These factors are such that acetylcholinesterase inhibitor exposure appears to be causally linked to illness in Gulf War veterans.

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APPENDIX D: INSTITUTE OF MEDICINE 1999 REPORT

In 1999 the Institute of Medicine recommended the creation of a National Center for Military Deployment Health Research, whose "oversight ... would include representatives of the VA and DoD, while ensuring that the center would be an independent as possible from direct control by these agencies." The recommendation further included "the participation of a broad set of constituencies, including veterans groups and the general public, on the Governing Board."

The IOM report recommended locating the Center within the Military and Veterans Health Coordination Board. Since that Board has been disbanded, an alternate location would need to be identified.

The Executive Summary of the Institute of Medicine study follows.

The full study can be found at www.nap.edu/html/military_deployment/center.pdf.

National Center for
Military Deployment Health Research

Lyla M. Hernandez, Catharyn T. Liverman, and Merwyn R. Greenlick, *Editors*

Committee on a National Center on
War-Related Illnesses and Postdeployment Health Issues
Division of Health Promotion and Disease Prevention

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Executive Summary

Concerns about the health of veterans of recent military conflicts have given rise to broader questions regarding the health consequences of service in any major military engagement. The Veterans Program Enhancement Act of 1998 directed the Secretary of Veterans Affairs to enter into an agreement with the National Academy of Sciences to help develop a plan for establishing a national center (or centers) for the study of war-related illnesses and postdeployment health issues. In response to this legislation, the Department of Veterans Affairs (VA) asked the Institute of Medicine (IOM) to convene a committee of experts. The charge to the committee was to (1) assist the VA in developing a plan for establishing a national center (or centers) for the study of war-related illnesses and postdeplovment health issues, and (2) assess preliminary VA plans and make recommendations regarding such efforts.

The IOM convened the Committee on a National Center on War-Related Illnesses and Postdeployment Health Issues, composed of experts on war-related illnesses, clinical research, military medicine, epidemiology, health services research, operations research, development of interdisciplinary research centers, research ethics, technology transfer, and the integration of clinical and education programs with research. Between January and September 1999, the committee met three times. The first meeting included a workshop that was held to obtain background information on relevant issues. During subsequent meetings, the committee reviewed information on war-related illnesses and relevant research activities, analyzed alternative models for national research centers, and received testimony from veterans about their views for such a center. Additionally, the committee examined the VA's proposal for developing a national center program within the VA.

The committee conducted its deliberations with an understanding that the nature of military engagement has changed. Contemporary military conflicts depend on the availability of smaller expeditionary forces that maintain a high level of military readiness. This greater reliance on readily deployable forces includes increased participation by guard and reserve members. Both active- duty, guard, and reserve forces experience profound life disruptions connected to all phases of deployment that, despite the relatively rapid and short-term experience, may have long-standing health consequences. Additionally, there is a component of deployed civilian workers who are similarly impacted by military deployment. The committee found that:

- Extensive research exists on the health of veterans of military conflict.
- The definition of deployment-related health issues selected for research has been too narrowly focused and has excluded some health consequences related to deployment.
- There are gaps in the emerging data relevant to the study of war-related illnesses and postdeployment health issues.
- Many investigations of health issues and effects of deployment have been mounted in response to health problems after they occurred, rather than being undertaken proactively.
- Many veterans and some congressional staff are skeptical of the objectivity of both the Department of Defense (DoD) and the VA in the conduct of research into deployment-related health issues.
- None of the locations of existing or proposed centers provides an adequate model for a national center that not only must be responsible for the conduct of a broad range of research but also must provide for synthesis and coordination of research efforts and for proposing policy changes based on research findings.
- Examples exist of centers that cut across agencies and groups to carry out effective research agendas.

VA PROPOSAL

One component of the committee's charge was to review the VA's proposal to establish Centers for the Study of War-Related Illnesses and Postdeployment Health Issues by using the model of the Geriatric Research, Education, and Clinical Centers (GRECCs). The GRECC program has been successful in training health professionals, conducting cutting-edge research, and implementing effective treatment programs. Creating centers based on this model for the study of deployment-related health should contribute greatly to the advancement of knowledge in this area. Therefore, the committee recommends that the Department of Veterans Affairs proceed with its proposal to establish centers for the study of war-related illnesses, and that these centers be similar in structure to the Geriatric Research, Education, and Clinical Centers.

NATIONAL CENTER

The second component of the committee's charge was to make recommendations regarding a national center. The committee concluded that a national center could provide the needed mechanism to coordinate and synthesize the ongoing research efforts. Such a center would be in a position to provide an overarching research agenda that would identify' gaps in current research, to coordinate existing and future research, to focus the infusion of new research funding, and to recommend policies related to such research. Therefore, the committee recommends that Congress establish a National Center for Military Deployment Health Research that will focus on the health of active, reserve, and guard forces, and veterans and their families.

Location of the National Center

Despite the anticipated contributions of the VA centers, location within the VA carries with it limitations for a national center that is responsible for coordinating and synthesizing research across federal agencies and in university-based settings. The committee examined a number of options for the location of the National Center and concluded that it should be independent of governance by any single federal agency in order to foster scientific excellence and assure scientific and public accountability. Therefore, the committee recommends that the National Center be placed under the auspices of and report to the Military and Veterans Health Coordinating Board (MVHCB). Further, the committee recommends that the National Center replace the Research Working Group of the MVHCB.

The MVHCB was established by Presidential Review Directive and is chaired by the secretaries of the Department of Defense, the Department of Veterans Affairs, and the Department of Health and Human Services. It is charged with providing “oversight, coordination, and linkages to other related efforts in the Federal Government in the areas of deployment health, health care, research, health risk communication and education, record keeping, and compensation." The MVHCB has a broader mission than is found in any single federal agency and has been mandated to foster collaborative effort.

The Research Working Group (RWG) of the MVHCB has been charged with providing recommendations and coordinating research activities on deployment health issues affecting active-duty members of the armed forces, veterans, and deployed civilians, as well as the families of these individuals; preventing unnecessary duplication of research and assuring that resources are directed toward high-priority studies; and with acting as a forum for information exchange within the research community at large and for research coordination among the three participating departments. Since the proposed National Center for Military Deployment Health

Research will encompass all aspects of the Research Working Group's mission, the committee suggests that the new Center replace the RWG, rather than duplicate its efforts.

The committee envisions three key structural components for the National Center. These components are:

- a Governing Board, composed of members of relevant constituencies, with responsibility for coordination and agenda-setting, as well as for oversight of the work of the Center;
- a Research Network that integrates research efforts in DoD, VA, HHS, universities, and other sites; and
- a core of specific functions, with appropriate staff to implement such functions, under the overall direction of the Center's board and the MVHCB director.

To assure the public, Congress, the scientific community, and others that all efforts of the Center are being conducted with the highest scientific integrity and public accountability, oversight of the Center should be by a Governing Board composed of representatives from a broad range of relevant constituencies.

Therefore, the committee recommends that the National Center Governing Board be composed of:

- three representatives each from VA, DoD, and HHS;
- six independent representatives from the research community; and
- six representatives from the community at large, including veterans and their families and the general public.

Additionally, the committee recommends that an independent scientific entity nominate, for both the research-community and the community-at- large positions, twice the number of candidates as there are positions available.

The committee recommends that the functions of the Governing Board include:

- development of a coordinated research agenda;
- commissioning of new research;
- creation of policies for the conduct and dissemination of Center re- search;
- evaluation of the output and productivity of Center research;
- development of policy recommendations that emerge from Center research;
- development of the Center's proposed annual budget; and
- preparation and transmittal to Congress of an annual report.

The committee has designed the research network of the National Center with two major components: (1) federal research programs and (2) Centerinitiated research. This structure provides minimum disruption to the ongoing research activities while adding a needed mechanism for research priority- setting and coordination, for dissemination of research results, and for undertaking tasks most appropriate for a central organization. Therefore, the commit- tee recommends a broad-based Center-initiated research program that would solicit proposals from federal agencies, universities, and other research sites and that would be managed by the National Center.

Center-initiated research should be implemented through the announcement of a set of Requests for Applications (RFAs) and Requests for Proposals (RFPs). It is suggested that the National Center enter into an agreement with the National Institutes of Health (NIH) to use the NIH peer-review process, to the extent possible, to assess the scientific merit of the applications and proposals. The final research funding decisions remain, however, the prerogative of the Center's Governing Board.

The committee recommends that the National Center be responsible for the four core activities:

- research coordination and priority setting;
- research-related policy analysis;
- review and analysis of longitudinal monitoring of deployment-related health; and
- facilitating the use of national data sources for deployment health re- search.

To foster research coordination and priority-setting, the Center should sponsor conferences and workshops to gather input for the research agenda and to encourage collaborative exchange. To increase scientific input in the development of the research agenda, the Governing Board may establish advisory groups or use other mechanisms to receive technical advice. It is anticipated that as the Center grows, so will its need for additional mechanisms to accomplish its activities. Rather than attempt to dictate those mechanisms, however, the committee believes it is important to allow the Board and staff to devise their own creative responses to their future needs.

Developing policy recommendations based on research results requires the synthesis and analysis of relevant research. Some of the same mechanisms described above for use in agenda-setting can be employed in policy analysis.

The committee identified the need for a mechanism to monitor the longitudinal health of active-duty, reserve, and guard forces that goes beyond the self-selected service members who participate in DoD and VA registries. A recently released IOM report (IOM, 1999) describes a research portfolio and longitudinal cohort study that could provide a model for a long-term tracking system of the health of veterans of military conflict. It is appropriate that the research described in that report fall within the purview of the National Center and become a cornerstone for its longitudinal monitoring efforts.

Given the numerous and varied data relevant to research on deploymentrelated health, the National Center should develop a process by which these data can be identified, inventoried, and described. Such activity will foster the effective use of these data.

Funding the National Center

The research issues involved in deployment-related health are complex and require long-term commitment if productive results are to be achieved. Significant funding resources will be needed for the National Center core activities, Governing Board, and Center-initiated research. The Center should propose a budget detailing the resources needed, and this budget should be a line item in the budget of the MVHCB. The Center should include such budget information in its annual report to Congress in order to provide that body with information about the functioning and productivity of the Center. Therefore, the committee recommends that the National Center should have a clear and distinct budget for its core activities and its Center-initiated research. Further, this budget should be a line item in the budget of the MVHCB.

CONCLUSION

Many have begun to ask whether there are health consequences of service in military conflicts beyond the obvious war injuries and, if so, whether there are ways to prevent or at least mitigate the consequences of war-related illnesses and deployment-related health effects. Congress directed that the Department of Veterans Affairs contract with the National Academy of Sciences to assist in developing plans for a national center (or centers) for the study of war-related illnesses and postdeployment health issues that could focus research on answering these questions.

The committee has recommended the establishment of a National Center for Military Deployment Health Research, to be governed by an independent board composed of representatives of the scientific community, the veterans' community, and relevant federal agencies. Such a center would provide an opportunity to gather together the results of many individual efforts, to analyze and synthesize what this research can reveal, and to move the nation forward in ways that will help and protect those individuals who will participate in future deployments.

The committee urges that the recommendations in this report be implemented as rapidly as possible in order to gain much-needed knowledge about how best to protect and treat the men and women who participate in military deployments.