Persian Gulf Veterans Coordinating Board – Research Working Group

Annual Report to Congress - 1997

Research on Gulf War Veterans' Illnesses

March 1998

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PERSIAN GULF VETERANS COORDINATING BOARD
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TABLE OF CONTENTS

EXECUTIVE SUMMARY

Introduction

On August 31, 1993, in response to Public Law 102-585, President William J. Clinton named the Secretary of Veterans Affairs (VA) to coordinate research funded by the Executive Branch of the Federal Government into the health consequences of service in the Gulf War. VA carries out its research coordinating role through the auspices of the Research Working Group (RWG) of the Persian Gulf Veterans Coordinating Board (PGVCB). The Secretaries of the Departments of Defense (DoD), Health and Human Services (HHS), and VA chair the PGVCB.

As part of its coordination role, VA is required to submit to the Veterans' Affairs Committees an annual report on the results and status of research activities. The Annual Report to Congress for 1997 is the fourth report on research and research activities.

In addition to the federally funded research efforts highlighted in this Annual Report, there are noteworthy research projects funded by sources other than the Executive Branch of the Federal Government. Because this research adds to, and builds upon, knowledge gained through federally funded efforts, the Annual Report for 1997 includes research findings of non-federally funded investigators published in peer reviewed scientific journals since the Annual Report for 1996.

The Annual Report for 1997 provides summaries of recently published research findings, an overview of the evolution and current status of the federal research portfolio on Gulf War veterans' illnesses, a discussion of significant research-related events and milestones since the Annual Report for 1996, and an overview of federal research management. The Appendix to the Report contains detailed supplemental information including brief descriptions of the research protocols; status and results of all ongoing and completed federally funded research projects; annual funding levels of research projects; abstracts from two major national scientific meetings; solicitations for new research; a strategic plan for research on health effects of low-level exposure to chemical warfare nerve agents; and a status report on development and use of experimental serological tests for leishmaniasis infection.

New Research Results

Since the Annual Report for 1996, a number of new research studies have been published which, along with previous research results, are helping to form a body of knowledge that will lead to reliable models of the health problems of Gulf War veterans. In addition, there have been some valuable preliminary findings reported at major scientific meetings. However, until peer-reviewed these findings must be treated with caution.

Before reviewing some of the findings, it is important to note that all research studies have strengths and limitations. Among the limitations, epidemiological studies are frequently subject to a variety of biases. For example, studies that rely on self-reported symptoms and exposures are subject to recall bias, and studies that rely on self-selected cohorts (such as registry participants) are subject to selection bias. Biases can distort the magnitude of differences between cohorts and affect the strength of associations between exposures and outcomes. Other factors potentially affecting epidemiological outcomes include sample size and response rate.

Research using animal models is also subject to limitations in its applicability to a specific situation for humans. Sources of limitations include extrapolation of biological processes from one animal species to another and extrapolation of experimental dosing regimens (route of administration, amount, and duration) in animals to real human exposure situations.

The presence of limitations in a particular study does not necessarily invalidate its findings or conclusions but must be taken into account in evaluating a study's overall weight and impact. For this reason, the strengths and limitations of each of the new reports of study findings are cited as a guide for the reader.

Brain and Nervous System

A number of papers focusing on neuropsychological performance, psychological health, and symptoms have been published. Although these studies suggest that a number of symptoms reported by Gulf War veterans may be

explained by psychological distress, evidence suggests that distress cannot explain all of the increased symptom reporting. In addition, new research in post-traumatic stress disorder (PTSD) is shedding new light on the nature, prevention, and treatment of the disorder. These findings will assist all veterans of deployments with this disorder, including Gulf War veterans. It will also contribute to the improvement of health outcomes in veterans of future deployments.

Chemical Warfare

Recent follow-up studies of victims of the sarin terrorist attacks in Matsumoto and Tokyo, Japan (two years and six to eight months following exposure respectively) are enhancing our understanding of the potential for long-term sequelae of exposure to sarin. A VA scientist collaborated in some of this work. The importance of these studies is the involvement of documented exposures to sarin. Results suggest that exposures causing immediate health responses may lead to persistent chronic effects in a dose-dependent fashion. These effects may vary from clinically undetectable (except through the use of highly sensitive measurement techniques) to clinically significant with overt signs and symptoms. These effects may not be related to the acutely toxic effects of cholinesterase reductions.

These findings are consistent with a DoD funded study in laboratory rats that reported that after anticholinesterase treatment when cholinesterase levels returned to pre-treatment control levels, learning deficits persisted in the animals. However, the rats studied were quite symptomatic when exposed.

The fact that these studies report long-term responses following acute exposures at levels sufficient to produce immediate observable effects somewhat diminishes the relevance to Gulf War veterans. However, the findings reinforce models of anticholinesterase toxicity that extend beyond the immediate effect and may not be directly related to cholinesterase inhibition.

Mortality

Preliminary results from a follow-up of the VA Mortality Study through 1995 show that disease-specific deaths do not occur at any greater frequency among Gulf War veterans than among their non-deployed counterparts. However, deaths by accidents, in particular motor vehicle accidents, are more frequent in Gulf War veterans. Preliminary results of a study examining the latter findings suggest that behaviors such as speeding and not wearing a seat belt may be contributing factors to the increased motor vehicle deaths among Gulf War veterans.

Reproductive Health

Two studies on reproductive health from the Naval Health Research Center in San Diego, CA indicate that there is no difference in the rates of birth defects in the offspring of Gulf War veterans compared to their non-deployed counterparts. A major study of discharge records (over 75,000 records) from military medical facilities found no difference in birth defects overall in the offspring of Gulf War veterans compared to non-deployed veterans. A substudy examining the rate of a rare birth defect known as Goldenhar Syndrome did not detect a statistically significant difference between the rate of Goldenhar Syndrome in the offspring of Gulf War veterans compared to non-deployed veterans. Additional studies are, however, continuing to pursue the question of adverse reproductive outcomes in Gulf War veterans.

Depleted Uranium (DU)

Preliminary results from a clinical follow-up study at the Baltimore VA Medical Center (VAMC) of 33 Gulf War veterans with embedded DU fragments show neither evidence of renal damage nor any other long-term consequences to date. This clinical study complements two important animal toxicology studies conducted by the Air Force Radiobiology Research Institute that examine cancer and non-cancer endpoints in laboratory animals with embedded DU

Symptoms/General Health

The undiagnosed illnesses of Gulf War veterans are still associated with a collection of self-reported symptoms and conditions that do not fit into a consistent pattern of disease. Consequently, research into the general problem of symptoms and general health status among Gulf War veterans is very important. A number of studies have reported notable findings this year.

Researchers are beginning to better understand the reliability of self-reported symptoms and exposures by conducting test-retest reliability studies, and exposure validation

studies. Unfortunately, preliminary results suggest that self-reported symptoms and exposures are inadequate measures of health outcomes and exposure for the purpose of epidemiological research. However, these studies will provide information to better interpret the findings of ongoing epidemiological studies that rely on self-reports. Also, these studies underscore the importance for future deployments of better pre-and post-deployment health assessments, and better quantitative exposure measures.

Based on self-reported symptoms and diagnoses relating to physical and mental health, the first completed study of women Gulf War veterans (done by a DoD funded researcher at the University of Michigan) suggests that women veterans may be experiencing some gender specific health problems at a greater rate than women veterans deployed elsewhere in the world during the Gulf War. Ongoing studies may shed additional light on the significance of these findings. Of particular note from this study, however, are the findings related to PTSD among women veterans. The Gulf War deployed women veterans had higher rates of PTSD compared to women veterans deployed elsewhere. Possibly of greater significance is the finding that both the Gulf War deployed women veterans and the women veterans deployed elsewhere had higher rates of PTSD than what would have been expected based on previous studies of mostly male veteran cohorts. This difference underscores the importance of studying the health problems of women in the military. This finding should be further examined in other ongoing studies of women's health in Gulf War veterans.

Funding of Federal Research

The federal research portfolio for Gulf War veterans' illnesses is diverse in its scope. Federally funded research covers an array of different exposures and health outcomes using epidemiological, clinical, basic, and developmental approaches, in particular vaccine and drug development.

Since 1994 the Federal Government has sponsored 121 research projects (with new projects about to begin) and has committed $115 million in resources to these projects (see Table ES-1). Over half of these projects involve scientists outside of the government. Through February 1998, 39 of the 121 projects have been completed, 78 projects are ongoing, and 4 have been awarded funds that are pending startup. Table ES-2 shows the number of projects completed and the number of newly funded projects by fiscal year since FY'94.

Table ES-1. Funding for Research FY'94-FY'98

Department	*FY'94*	*FY'95*	*FY'96*	*FY'97*	**FY'94-97 Total**	**FY'98 (Proj.)**
DoD	$5.9	$12.5	$12.3	$31.8	**$62.5**	**$20.2**
VA	$1.2	$2.3	$4.9	$2.4	**$10.8**	**$16.5**
HHS		$2.5	$1.6		**$4.1**	**$1.2**
Total	$7.1	$17.3	$18.8	$34.2	**$77.4**	**$37.9**

Figure ES-1 shows the trend over time from 1994 through 1998 of the number of active research projects taking different research approaches.

Table ES-2 Number of New and Completed Projects by Year

Fiscal Year	*New*	*Completed*
1994	20	3
1995	33	8
1996	22	4
1997	14	15
1998	14**	21*

*Projected for all of FY'98
**Does not include projects starting after 3/1/98 nor projects under final negotiation

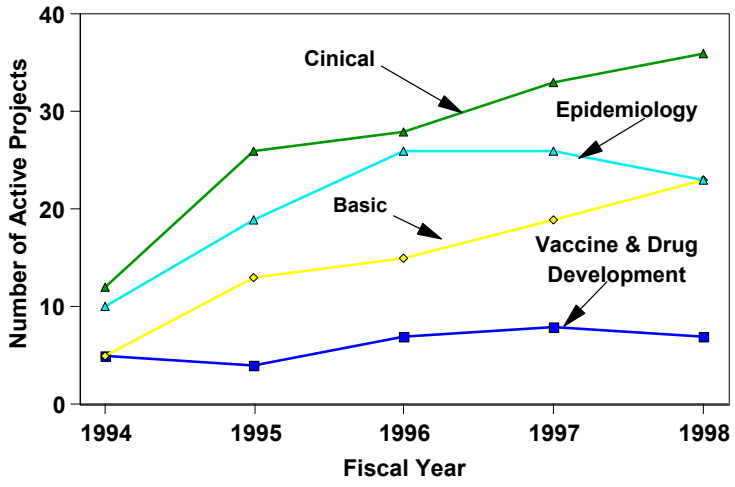

Figure ES-1. Number of active research projects of different types for each fiscal year

As the number of active research projects has increased from 32 in 1994 to as many as 90 in 1998, the patterns of investment have changed. The proportion of research projects funded in epidemiology research has appropriately declined while the number of research projects on chemical weapons, both in relative and absolute terms, has markedly increased.

Beginning in 1998 new research will begin to focus on clinical trials for treatment of Gulf War veterans. VA and DoD have invested approximately $10 million in what may be the single largest treatment trial of Chronic Fatigue Syndrome and Fibromyalgia in the United States. In addition to treatment, future research investments will increasingly serve both the needs of Gulf War veterans and those of participants in future deployments.

Figure ES-2 shows the cumulative investment in research across various areas of research focus. The nature of each research funded research project in the portfolio described by up to three focus areas, as appropriate. Figure ES-2 shows the investments according to the primary focus area of each project, and according to all focus areas assigned to each project. The investment of funds has been greatest in the focus areas of the Brain and Nervous System and in Symptoms and General Health. The third largest investment is in the focus area of Diagnosis that is research directed toward characterizing Gulf War veterans' illnesses, and on specific diagnostic tests such as the research on a serological assay for leishmaniasis.

The distribution of research projects across various research focus areas has changed over time since 1994 as a reflection of the evolution of issues centered on Gulf War veterans' illnesses. There has been a relatively greater increase over the years of research on chemical interactions, chemical warfare agents and pyridostigmine bromide. These increases are an outgrowth of increased concern over the health risks posed to veterans by exposures to multiple toxic agents at low-levels. It is significant to note that of all potential etiologic agents, the largest investment in research on chemical weapons.

New Research Projects, Initiatives, and Milestones

In addition to new research results, a number of new research projects and initiatives have been started, and some significant milestones

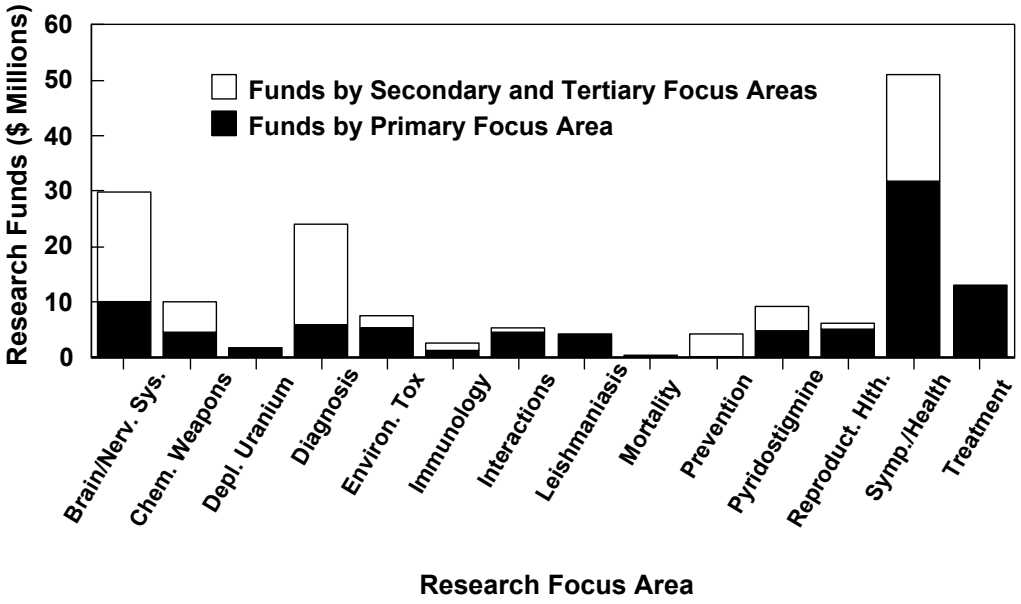

Figure ES-2. Research costs by research focus areas

have been reached. Many of the new research projects and initiatives are the direct result of recommendations from a variety of sources including the Presidential Advisory Committee on Gulf War Veterans' Illnesses (PAC, 1996b), the Institute of Medicine Panel on the Health Consequences of Service in the Persian Gulf War (IOM, 1996), and the RWG (PGVCB, 1995, 1996b)

- DoD funded 12 new research projects on the health effects of low-level exposures to chemical war nerve agent, interactions of multiple chemical stressors, and other new research;
- CDC funded two major cooperative agreements with Boston University and the University of Medicine and Dentistry of New Jersey, Robert Wood Johnson Medical School to study in depth the characteristics of Gulf War veterans illnesses and to attempt to develop a case definition;
- The Iowa Study of Gulf War Veterans will be extended to include physical examinations on a subset of participants in the original project;
- The Medical Follow-Up Agency of the Institute of Medicine will conduct an epidemiological investigation of the health of troops potentially exposed to sarin as a result of the demolition of a weapons depot in Khamisiyah, Iraq in March, 1991;
- VA and DoD will begin collaboration on the development and implementation of a multi-site treatment trial for Gulf War veterans with Chronic Fatigue Syndrome and Fibromyalgia;
- VA issued a Program Announcement (an open-ended request for proposals) soliciting proposals for additional treatment trials for Gulf War veterans' illnesses;
- Following scientific peer-review and programmatic review, VA and DoD will be funding new research projects on the neurobiology of stress;

- DoD is providing funding for follow-up studies of research reported in the *Journal of the American Medical Association* in January 1997 that suggest the presence of neurological problems in Gulf War veterans possibly associated with exposure to neurotoxins;

- Research will attempt to validate a test for mycoplasma infection and, once validated, be used to investigate suggested links among service in the Gulf, mycoplasma infection, and symptoms;

- The Research Working Group developed a *Strategy for: Research on the Health Effects of Exposure to Low-Levels of Chemical Warfare Nerve Agents*;

- VA researchers developed Phase III of the VA National Survey of Gulf War Veterans, which is the last phase of this major population-based survey;

- A plume model was developed and peer-reviewed for estimation of troop exposure to sarin from the Khamisiyah, Iraq demolition;

- The Research Working Group conducted an evaluation of the status of research on serological testing for leishmaniasis; and

- DoD issued a Broad Agency Announcement for $8 million in additional research on the pathogenesis of Gulf War veterans' illnesses, and on methods to prevent such occurrences in future deployments. Proposals were due February 4, 1998.

- DoD established a dedicated program element for GWVI research beginning in FY '99, with FY '98 being the transition year. This should improve DoD oversight and expedite Congressional review since program accomplishments, plans and resource information will be centrally documented.

- DoD chartered a Working Integrated Process Team (WIPT) on Deployment Toxicology. The WIPT will review current deployment toxicology initiatives and develop recommendations regarding appropriate DoD-level sponsorship and oversight of related policy issues, doctrinal matters, and requirements generation. Such initiatives are essential for protecting the forces during future deployments.

- DoD incorporated review of DoD-sponsored research on Gulf War veterans' illnesses in the annual Technology Areas Review and Assessment process. This review is utilized by DoD to obtain advice and recommendations on its science and technology programs and utilizes the expertise of independent technical experts.

I. INTRODUCTION

On August 31, 1993, in response to Public Law 102-585, President William J. Clinton named the Secretary of Veterans Affairs (VA) to coordinate research funded by the Executive Branch of the Federal Government into the health consequences of service in the Gulf War. VA carries out its research coordinating role through the auspices of the Research Working Group (RWG) of the Persian Gulf Veterans Coordinating Board (PGVCB). The Secretaries of the Department of Defense (DoD), Health and Human Services (HHS), and VA chair the PGVCB.

In its role as research coordinator, VA is required to submit to the Veterans' Affairs Committees an annual report on the results and status of research activities. This document, the 1997 Annual Report to Congress, is the fourth report on research and research activities.

This edition of the Annual Report to Congress reports on research funded by federal and non-federal institutions. All new peer-reviewed reports of high quality research, regardless of funding source, add to and build upon existing knowledge. Unpublished research results may be discussed with the anticipation of publication in the open peer-reviewed literature. However, the use of non-peer-reviewed results is done with caution and does not have the weight of peer-reviewed research results.

This Annual Report is divided into five sections. Following this section, Section II highlights and summarizes research progress since the last Annual Report. Section III is an analysis of the Federal Government's portfolio of research on Gulf War veterans' illnesses. Section IV highlights significant research and research-related events and milestones since the last Annual Report. Section V discusses the management of federal Gulf War veterans' illnesses research programs, including research oversight, peer-review and coordination.

II. RESEARCH RESULTS IN 1997

A. New Research Publications

In the past year there have been several research studies that have yielded results that provide new and expanded information on the health problems of Gulf War veterans. This section provides brief summaries of research projects for which results have become available in the past year. Because all credible, scientifically peer reviewed research must be considered in any future science-based assessments of Gulf War veterans' illnesses, these summaries are inclusive of both federally funded and non-federally funded research. The primary source of information on non-federally funded research is from the peer-reviewed scientific literature. The RWG tracks all federally funded research projects reported to the RWG related to Gulf War veterans' illnesses. These projects are described in greater detail in Appendix A.

It is important to note that all research studies have strengths and limitations. Among the limitations, epidemiological studies are frequently subject to a variety of biases. For example, studies that rely on self-reported symptoms and exposures are subject to recall bias, and studies that rely on self-selected cohorts (such as registry participants) are subject to selection bias. Biases can distort the magnitude of differences between cohorts and affect the strength of associations between exposures and outcomes. Other factors potentially affecting epidemiological outcomes include sample size and response rate.

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The presence of limitations in a particular study does not necessarily invalidate its findings or conclusions but must be taken into account in evaluating a study's overall weight and impact. For this reason, the strengths and limitations of each of the new reports of study findings are cited as a guide for the reader.

In previous reports to Congress and other publications, research has been categorized according to the particular focus of the research. The research reports summarized below are grouped according to those focus areas, which are defined in Section III-1.

1. Brain and Nervous System

Neuropsychological Findings in a Sample of Operation Desert Storm Veterans (Federally Funded)

In two papers published in 1997 (Sillanpaa et al., 1997; Axelrod and Milner, 1997) investigators at the Allen Park, MI VA Medical Center (VAMC) reported on the results of comprehensive neuropsychological evaluation in a small group (44) of volunteer Gulf War veterans. The researchers compared their findings with normative population data. In this group of treatment-seeking veterans, they found that out of 36 tests examining different neuropsychological domains, there were statistically significant deficits relative to normative data only on finger dexterity and a single test of brain executive function. Veterans with impaired finger dexterity performance also had lower performance scores on other tasks requiring psychomotor speed when compared with normative data. Those with impaired executive function as indicated by one test, had significantly poorer psychomotor performance. Investigators also administered the Minnesota Multiphasic Personality Inventory (MMPI) to assess psychological status. When compared with normative data, the groups who performed below normal on the finger dexterity or on the test of executive function scored higher (more poorly) on many clinical and supplemental scales of the MMPI. Overall the researchers observed that subjective cognitive complaints were reported in 39% of their sample. However, the veterans with cognitive complaints were primarily different from the other veterans studied by having greater psychological distress as measured by MMPI.

This investigation is difficult to generalize to Gulf War veterans because it involved a small number of self-selected Gulf War veterans and there was no control group. The study is also limited in that comparisons of many tests with normative data were performed. Chance alone could account for the observed differences. Nevertheless, differences were consistent within the psychomotor and executive function tests. Lastly, conclusions were drawn using comparisons of outcomes to normative data, and not to a control group.

With these reservations in mind, the investigators concluded that psychological distress may account for the observed deficits in neuropsychological performance.

Neuropsychological Correlates of Gulf War Syndrome (Non-Federally Funded)

Hom et al. (1997) have provided a more detailed report on the neuropsychological component of research they had earlier reported (Haley et al., 1997a,b; Haley and Kurt, 1997). Investigators tested neuropsychological and psychological performance in 26 ill Gulf War veterans from the 24th Reserve Naval Mobile Construction Battalion (RNMCB-24). The control groups consisted of 10 healthy deployed members of the same battalion, and 10 healthy non-deployed battalion members. The controls were selected to have similar demographic characteristics as the 26 study subjects. The study subjects were selected from a larger pool of 249 veterans who participated in a self-reported health survey conducted by Haley et al. (1997a). In the latter study, factor analysis was applied to the self-reported symptoms in an attempt to identify a syndromic pattern(s). Six factors were found to explain 71% of the variance among self-reported symptom responses. The 26 study subjects in the report summarized here were drawn from the most symptomatic veterans based on a factor-derived definition of illness.

Each subject was administered a comprehensive battery of neuropsychological tests. Over three dozen test scores examined different brain function domains. In addition to the neuropsychological tests that were administered, subjects were also administered the Personality Assessment Inventory (PAI) to determine psychological status.

Hom et al. (1997) found statistically significant differences between the 26 ill veterans and the 20 control veterans in 2 out of 9 tests of generalized brain function. Performance on all tests of generalized brain function was, however, moderately impaired in the ill group of veterans. With respect to specific brain performance the investigators found no consistent pattern of deficits, which means no involvement of a particular area of the brain or

brain hemisphere. Study and control group measures were within one standard deviation of each another (including those that are statistically significantly different).

It should be noted, though, that the lack of a consistent pattern in specific brain function deficits is not congruous with the types of neurotoxicants to which troops were exposed in the Gulf. Such neurotoxicants produce more specific and consistent patterns of brain function deficit between subjects.

Results of the PAI showed that ill veterans were statistically significantly higher (meaning poorer psychological health) on 9 out of 19 measures in comparison with the control group. Hom et al. (1997) speculate that the observed neuropsychological deficits are indicative of neurotoxic injury related to service in the Gulf War in some veterans.

This study is similar in the outcomes studied as that of Axelrod and Milner (1997) and Sillanpaa et al. (1997) summarized above. The one advantage over the previous study is the use of a control group. Although a comparison of these two studies is difficult because they represent two different populations, some observations can be made. In both cases there are a small number of neuropsychological deficits among self-reporting Gulf War veterans. In addition both studies found evidence of elevated psychological distress. Most importantly, however, is the finding by the investigators that the deficits are not clinically significant.

Assessment of Intellectual Resources in Gulf War Veterans: Relationship to PTSD (Federally Funded)

Past research on PTSD indicates that individual difference factors may alter the vulnerability of an individual to trauma-related distress. Vasterling et al. (1997) have investigated the potential buffering effects of an individual's intellectual resources on PTSD development. To accomplish this they assessed intellectual functioning in subsets of Gulf War veterans with and without PTSD diagnoses. The veterans were drawn from a community-based sample of Gulf War veterans. The two subsets, comprised of 18 PTSD-diagnosed and 23 psychopathology-free Gulf War veterans, were compared on multi-faceted tests of intellectual functioning. As compared to psychopathology-free veterans, PTSD-diagnosed veterans did not perform as well (at statistically significant levels) on *verbal* subtests of the Wechsler Adult Intelligence Scale (Revised). However, there were no differences on *performance* subtests. Across the entire sample, correlational analysis showed that *verbal* subtest scores were inversely correlated with the severity of PTSD symptomatology. However, neither *performance* subtest scores nor war zone stress exposure was related to PTSD symptom severity.

Because this was not a prospective longitudinal study, it could not definitively determine the direction of causality. However, the fact that *performance* subtest scores were not different between the two groups suggests that intellectual resources, particularly verbal skills, may buffer development of stress-related psychopathology following trauma exposure. Small sample size is a limitation to this study.

Attention and Memory Dysfunction in PTSD (Federally Funded)

Vasterling et al. (1998) investigated neuropsychological conceptualizations of PTSD, by examining attention and memory performances in a community-based sample of Gulf War veterans with (N=19) and without (N=24) PTSD diagnoses. Attention measures involved four components with two measures each.

Multivariate analyses show that PTSD-diagnosed veterans were statistically significantly different from their psychopathology-free counterparts in both attention performances, and learning and memory performances. More specifically, PTSD-diagnosed veterans displayed relative deficiencies on measures of sustained attention and mental manipulation of information, but not on measures of selective attention or flexibility in shifting attention. On memory performances, PTSD-diagnosed veterans demonstrated relative deficiencies in initial acquisition of information and heightened sensitivity to retroactive interference, but not on measures of memory savings and sensitivity to proactive interference. These cognitive deficit patterns are consistent with models of PTSD that emphasize the role of hyperarousal and implicate dysfunction of frontal-subcortical systems. Results suggest that intrusion of traumatic memories in PTSD may not be limited to trauma-related cognitions but instead reflects a more general pattern of

disinhibition (the inability to prevent intrusive memories).

Consistency of Memory for Combat-Related Traumatic Events in Veterans of Operation Desert Storm (Federally Funded)

Southwick et al. (1997) investigated the temporal nature of traumatic memories in Gulf War veterans with PTSD. It has been a question of debate whether traumatic memories are fixed over time or are malleable and subject to distortion and alteration. To address this question, these investigators conducted a prospective investigation of memory for serious combat-related traumatic events in Gulf War veterans. Fifty-nine National Guard reservists from two separate units completed a 19-item trauma questionnaire about their combat experiences 1 month and 2 years after their return from the Gulf War. Responses were compared for consistency between the two time points and correlated with level of symptoms of PTSD. The researchers found that there were many instances of inconsistent recall for events that were objective and highly traumatic in nature. Eighty-eight percent of subjects changed their responses on at least one of the 19 items, while 61% changed two or more items. There was a significant positive correlation between score on the Mississippi Scale for Combat-Related Posttraumatic Stress Disorder at 2 years and the number of responses on the trauma questionnaire that changed from "no" at 1 month to "yes" at 2 years. These findings do not support the position that traumatic memories are fixed or indelible, but that as PTSD symptom levels increase, so does amplification and distortion of memory for traumatic events. This study raises questions about the accuracy of recall for traumatic events, as well as about the well-established but retrospectively determined relationship between level of exposure to trauma and PTSD symptoms levels.

2. Chemical Weapons Exposures

Neurobehavioral and Neurological Effects of Tokyo Sarin Poisoning (Non-Federally Funded)

Researchers with the University of Tokyo, St. Lukes Hospital in Tokyo, and Boston University (and Boston VAMC) have reported on the results of studies of 18 (9 male and 9 female) subjects 6-8 months following their poisoning in the Tokyo subway sarin attack of March, 1995 (Yokoyama et al., 1998a,b; Murata et al., 1997). The report of Yokoyama et al. (1998a) focuses on neurobehavioral outcomes whereas the papers of Murata et al. (1997) and Yokoyama et al. (1998b) focus on neurophysiological outcomes.

On the day of the poisoning, 15/18 of the subjects had serum cholinesterase levels < 100 IU/l (normal range 100-250 IU/l). All subjects were symptomatic upon admission to the emergency room on the day of the attack. These studies used a matched set of non-exposed control subjects for comparison.

In the study of Yokoyama et al. (1998a) the 18 subjects were examined using 9 neurobehavioral tests, General Health Questionnaires (GHQ), the Profile of Mood States (POMS), and a posttraumatic stress disorder (PTSD) checklist modified for the sarin incident. Using covariate analysis, controlling for age, educational level, alcohol consumption and smoking (covariates), the researchers found that in the 18 sarin cases one measure of psychomotor performance (digit-symbol test) was significantly lower compared to controls. Scores on GHQ, the fatigue scale of POMS, and PTSD were significantly higher. When PTSD was added to the covariates, only the score on psychomotor performance was significantly lower in sarin cases. The researchers also found that scores on GHQ, POMS, and the paired-associate learning test were significantly related to PTSD symptomatology. On the other hand, the score on the digit-symbol test was not significantly related to PTSD.

It was suggested that a chronic effect on psychomotor performance was directly caused by acute sarin poisoning. The effects on psychiatric symptoms, and fatigue, however, were seen as being related to PTSD rather than as a toxic effect of sarin exposure.

The neurophysiological research of Murata et al. (1997) hypothesized focal or functional brain deficits 6-8 months following exposure to sarin. The subjects studied were the same as in the neurobehavioral testing protocol. The event-related and visual evoked potentials (P300 and VEP), brainstem auditory evoked potential (BAEP), and the variability of the electrocardiographic R-R interval ($CV_{RR,}$ a measure describing the variability of heart rate), together with the score on the posttraumatic stress disorder (PTSD) checklist, were measured

in the sarin cases and the same number of control subjects matched for sex and age.

Although none of the sarin cases had any obvious clinical abnormalities at the time of testing, various brain electrophysiologic measures were different compared to controls.

The P300 and VEP (P100) latencies in the sarin cases were significantly prolonged compared with the matched controls. These latencies are thought to reflect cognitive function and conduction time from retina to visual cortex respectively. In the sarin cases, the variability of heart rate was higher in individuals who had higher levels of cholinesterase (ChE) determined immediately after exposure. It is not clear what this finding means. PTSD scores were not associated with any neurophysiological data despite the high PTSD scores in the sarin cases.

These findings suggest that individuals without overt symptoms 6-8 months following the sarin exposure, which initially was at levels sufficient to produce acute symptomatic responses, persist demonstrating higher cortical and visual nervous system effects after the recovery of normal ChE levels. Furthermore, these sequelae do not appear to be related to PTSD. This research indicates that sarin may have neurotoxic actions in addition to the acute inhibitory action on brain ChE.

An additional preliminary study of the 18 Tokyo subway victims (Yokoyama et al., 1998b) provides suggestive evidence that acute sarin poisoning may also affect the vestibulo-cerebellar system 6-8 months following exposure. Using computerized static posturography, the researchers found that the nine female subjects had greater low-frequency sway when standing still compared to controls. There was no difference between poisoned males and controls. However, in both males and females, a measure of sway was correlated with serum ChE levels at the time of poisoning. These findings suggest the presence of another subclinical delayed effect of sarin exposure following poisoning that caused acute frank signs and symptoms indicative of a cholinergic crisis.

Clinical Follow-up of Sarin Poisoning in Matsumoto Japan (Non Federally Funded)

In 1994, a sarin attack in Matsumoto, Japan killed 7 residents and poisoned approximately 500 others. Investigators from Shinsu University School of Medicine in Matsumoto conducted follow-up clinical studies of 264 treatment-seeking, acutely symptomatic victims at 1 and 3 months following the attack (Morita et al., 1995). Although at 1 month, subclincial miosis and neuropathy were present in some patients, by 3 months virtually all studied patients had recovered. To investigate clinical sequelae at a longer point in time, Sekijima et al. (1997) conducted 1-year and 2-year follow-up health examinations of all victims who showed a decrease in serum cholinesterase (ChE) activity or miosis during the acute phase.

One hundred forty-nine victims met inclusion criteria. Of these, 85 (57.0%) had follow-up examinations. The investigators subdivided the patients into 3 groups according to the percentage of the minimum value for normal ChE (ChE%) that was measured during the acute phase. Six (6) persons were in the **severely poisoned** group (ChE% < 25%), 27 in the **moderately poisoned** group (ChE%, 25% to <100%), and 52 in the **mildly poisoned** group (ChE% >= 100% or not examined). All severely poisoned victims still showed abnormal clinical findings at the 1 or 2 year follow-up time. Four of 6 severely poisoned persons still showed epileptic electroencephalographic changes, which were the most characteristic abnormality. Other abnormal findings, such as arrhythmia, hypoxia or low-grade fever, also continued to be seen in three of the severely poisoned group. One of the severely poisoned victims developed sensory polyneuropathy 7 months after the exposure, and sensory nerve conduction velocity was reduced. In the moderately poisoned group, one victim continued to have visual defects at the 1-year follow-up health examination. However, this patient recovered completely 17 months after the exposure. The other moderately poisoned victims and all of the mildly poisoned victims showed no objective abnormal findings. As with the studies on the Tokyo subway victims, the investigators concluded that acute exposure to high levels of sarin, which were sufficient to induce severely acute symptoms and significantly reduce ChE levels, can cause clinically measurable sequelae for a longer period of time following exposure than had been previously known.

Chronic, Low-Level Exposure to Diisopropylfluorophosphate (DFP) Causes Protracted Impairment of Spatial Navigation Learning (Federally Funded)

Researchers at the Medical College of Georgia and the Augusta, GA VAMC (Prendergast et al., 1997) studied the effect of subchronic (14 days) exposure to the organophosphate (OP) diisopropylfluorophosphate (DFP), which like sarin inhibits acetylcholinesterase (AchE) activity. The overall purpose of the study was to identify the severity of impairment in spatial learning of rats following 21-day withdrawal from the 14-day exposure. Different groups of rats were exposed by injection to 50, 250, or 500 μg/kg body weight of DFP for 14 days. The investigators then assessed spatial learning at either 3 or 17 days after completion of a 14-day DFP treatment regimen. Spatial learning was assessed using a water maze in which the rats had to find a submerged platform.

At all doses during the 14-day treatment regimen, spontaneous motor activity and olfactory (sniffing) behaviors were affected. At the 250 μg/kg and 500 μg/kg dose regimens, spontaneous activity and olfactory behaviors decreased. These effects subsided upon repeated exposure at the 250 μg/kg dose but not at the 500 μg/kg dose. In contrast, both behaviors were stimulated by exposure to the 50 μg/kg dose regimen. Rats administered 500 μg/kg could not be studied in the water maze because of muscle fasciculation. Furthermore, about 40% of the rats receiving the high dose and 5% of the rats receiving the medium dose experienced fasciculations, weakness, and anorexia sufficient to cause death or necessitate euthanasia.

The investigators found that performance of the spatial test of working memory was impaired for up to 21 days after withdrawal from the 250 μg/kg dose regimen of DFP. They also measured AChE activity in the frontal cortex and hippocampus, and found that both levels were depressed relative to controls 3 days after completion of the 250 μg/kg dose regimen. By 7 days after withdrawal from treatment, AChE activity in the cortex and hippocampus had recovered to 81.87% and 64.61% of control levels, respectively. By 21 days after withdrawal from treatment, AChE in both brain regions had recovered to levels similar to those of controls.

It is difficult to extrapolate the results of this study to long-term effects of possible sarin exposure in Gulf War veterans. First, the investigators used repeated, relatively high dosing by injection. Second, the chemical activity of DFP is analogous but not identical to sarin. Lastly, the use of a rat model also makes extrapolation to humans difficult. At the lowest doses, the rats did not show signs of acute toxicity or memory impairment.

Given the above limitations, this research shows that subchronic OP exposure can produce impairment of working memory three weeks after cessation of exposure. This is not associated with continued suppression of AChE activity. The investigators speculate that this impairment may be associated with a decreased rate of AChE recovery in the hippocampus relative to the cortex and may contribute to hippocampal toxicity underlying impairment of working memory.

A New Technique to Retrospectively Identify and Quantify Sarin Exposure (Federally Funded)

Quantitatively ascertaining an individual's exposure to an organophosphate, in particular one such as sarin, after exposure has occurred is difficult. Blood or serum acetylcholinesterase activity following an exposure is the standard exposure biomarker. However, acetylcholinesterase levels begin to return to normal within hours after exposure making this a poor exposure marker at long times following exposure. In addition, present methods can neither detect low-level exposures with certainty nor identify the structure of the agent and the extent of poisoning.

In contrast to organophosphate inhibited acetlycholinesterase activity, organophosphate-inhibited butyrylcholinesterase in human plasma appears to be persistent and abundant as a source for exposure biomonitoring for many days. Researchers at TNO Prins Maurits Laboratory in The Netherlands used fluoride ions to reactivate the inhibited enzyme, thus releasing the bound anticholinesterase (such as sarin). Subsequent quantitative analysis of the latter product provides a reliable, highly sensitive and retrospective method for direct detection of exposure to organophosphates such as nerve agents and organophosphorus pesticides. Polhuijs et al. (1997) applied this new procedure to serum samples from victims of the Tokyo subway sarin and from an earlier sarin attack at

Matsumoto. In serum of 10 of 11 victims from the Tokyo incident and of 2 of the 7 samples from the Matsumoto incident, reactivation with fluoride ions yielded measurable amounts of sarin. Evidently, these victims had been exposed to an organophosphate with the structure CH_3-P(=O)(-F)(-$OCH(CH_3)_2$). This research represents an important advance in the development of chemical warfare nerve agent biomarkers as was recommended in the *Working Plan for Research on Persian Gulf Veterans' Illnesses* (PGVCB, 1996b).

3. Pyridostigmine Bromide

PB May Cause Reduction in Pyrethroid Concentration in the Central Nervous System (Federally Funded)

Researchers at Lawrence Livermore National Laboratory studied the effect of the pyridostigmine bromide (PB) on the uptake of carbon-14 labeled permethrin by the central nervous system (CNS) (Bucholz et al., 1997). It has been asserted that the interactions among PB, permethrin (a pyrethroid insecticide), and DEET (an insect repellent) may have caused long-term health effects in Gulf War veterans in spite of the low toxicity of each of these chemicals individually. PB was administered in food to four rats at scaled human-equivalent doses of 7.75 mg/kg per day for 10 days (the prescribed dose for troops in the Gulf War was about 1.3 mg/kg per day body weight). Five rats were given untreated food over the same period. At the end of the 10 day period each rat was administered 4.75 μg/kg of C-14 labeled permethrin by injection. Using accelerator mass spectrometry (AMS), the investigators measured concentrations of permethrin in the brain, spinal cord, and plasma of rats at 1 hour and 24 hours following injection. Pyridostigmine bromide lowered the tissue levels of permethrin in the CNS of rats by 30%. These results suggest that pretreatment with PB may inhibit uptake of pyrethroids in the CNS, thus possibly mitigating against CNS effects rather than enhancing them. Weaknesses of this study include the small number of rats studied, and the relatively high dose of PB administered. The study does, however, add new information to the issue of potential interactions among possible exposures in the Gulf War.

4. Reproductive Health

THE RISK OF BIRTH DEFECTS AMONG CHILDREN OF PERSIAN GULF WAR VETERANS (Federally Funded)

Gulf War veterans have expressed concern over the potential effects of Gulf War service on their offspring. To address this concern, Cowan et al., (1997) examined routinely collected data on all live births at 135 military hospitals in 1991, 1992, and 1993. Administrative records included up to eight diagnoses from the *International Classification of Diseases, 9th Revision, Clinical Modification* (ICD-9-CM) for each birth hospitalization. The records also contained information on the demographic characteristics and service history of the parents. The records of over 75,000 newborns were evaluated for any birth defect (ICD-9-CM codes 740 to 759, plus neoplasms and hereditary diseases) and for birth defects defined as severe on the basis of the specific diagnoses and the criteria of the Centers for Disease Control and Prevention. The researchers found that during the study period, 33,998 infants were born to Gulf War veterans and 41,463 were born to non-deployed veterans at military hospitals. They found that the overall risk of any birth defect was 7.45 %, and the risk of severe birth defects was 1.85 %. These rates are similar to those reported in civilian populations. In the multivariate analysis, there was no association for either men or women between either service overall in the Gulf War or time of service and the risk of any birth defect or of severe birth defects in their children.

The researchers conclude that there is no evidence of an increase in the risk of birth defects among the children of Gulf War veterans, but they also recommend a conservative approach to interpreting the data because of limitations of the study. First, not all births during this time occurred in military hospitals. It is possible that some difficult pregnancies involving high risk mothers or fetuses were seen at non-military hospitals. Second, the study captured only records of active duty service members during the study period. Third, many minor birth defects are not diagnosed until some time after birth and thus may have not been recorded at the time of birth. Last, the study only had sufficient statistical power to detect differences in overall birth defect rates. It did not have adequate power to focus on specific birth defects. Despite these drawbacks, this is

the first population-based study to examine the prevalence of birth defects among Gulf War veterans.

Goldenhar Syndrome among Infants Born in Military Hospitals to Gulf War Veterans (Federally Funded)

In addition to the general concern about birth defects expressed by Gulf War veterans, there has been specific concern over the defect known as Goldenhar syndrome. Goldenhar syndrome is a disorder characterized by abnormal prenatal development of facial structures. It is included under a broader category known as the oculo-auricuolo-vertebral (eye-ear-spine) spectrum. Although there are no agreed upon diagnostic criteria for Goldenhar syndrome, it is generally agreed that a small or missing ear(s) or skin tags in front of the ear are necessary for the diagnosis. Other components include asymmetry or arrested development of the jaw, and selected eye, vertebral, and facial anomalies.

In a study of hospital discharge records of 75,414 infants conceived after the Gulf War and born in military treatment facilities (34,069 infants born to Gulf War veterans, and 41,345 born to non-deployed veterans), Araneta et al. (1997) found no statistically significant difference in the prevalence of Goldenhar syndrome in infants born to Gulf War veterans compared to non-deployed veterans. Two pediatricians with expertise in clinical genetics, dysmorphology, and epidemiology conducted extensive reviews of the medical records. The pediatricians were blinded with respect to whether an infant was from a Gulf War veteran's family or from that of an era veteran. They determined that five infants with Goldenhar Syndrome were born to Gulf War veterans and two infants with Goldenhar Syndrome were born to non-deployed veterans for prevalences of 14.7 per 100,000 live births compared to 4.8 per 100,000 live births respectively. Each pediatrician independently identified the same cases as Goldenhar syndrome. The different number of Goldenhar syndrome cases in Gulf War veterans compared to era veterans was not statistically significant. However, the small number of births with Goldenhar syndrome in these two groups means that chance cannot be ruled out as an explanation for these findings. Other limitations of this study are similar to those in the Cowan et al. (1997).

The cause of Goldenhar syndrome in the general population has not been clearly elucidated. Moreover, all 7 case infants had fathers who served in the military. At this time paternal exposure has yet to be clearly established as a cause of birth defects, in general.

Consequently, the results of this study are somewhat reassuring regarding the occurrence of this birth defect among Gulf War veterans.

5. Symptoms/General Health

Relationship between Posttraumatic Stress Disorder and Self-Reported Physical Symptoms in Persian Gulf War Veterans (Federally Funded)

Prior research has shown that combat veterans with PTSD report more physical symptoms compared to veterans without PTSD. Such a link between PTSD and somatic complaints in Gulf War veterans has not, however, been fully evaluated.

Baker et al. (1997) of the Cincinnati VAMC administered a questionnaire to 188 Gulf War veterans, of whom half were patients in a veterans health screening clinic and half were non-treatment-seeking volunteers on active duty. The questionnaire included the Combat Exposure Scale, the Mississippi PTSD Scale (MPTSD), and a subjective symptom-based health questionnaire.

These investigators found that the 24 Gulf War veterans (12.8%) with PTSD (MPTSD score >=116) reported statistically significantly more combat exposure and a greater number of physical symptoms than other Gulf War veterans. Fatigue, nausea, muscle aches, dizziness, back pain, stomach ache, and numbness were much more likely to be reported by those with PTSD (MPTSD score >=116) than by those without PTSD (MPTSD score <=95).

This study does not shed any light on the prevalence of PTSD in Gulf War veterans, nor does it suggest that the symptomatic complaints of Gulf War veterans are mostly explained by PTSD. This study does, however, provide important information for physicians examining Gulf War veterans. The investigators suggest that examining physicians should be alert to the possibility of PTSD in this group. Diagnosis of other coexisting conditions may be confounded by the presence of PTSD and early effective treatment of their PTSD could be delayed as a

consequence. This study also stresses the importance of controlling for PTSD in studies examining symptom complexes in Gulf War veterans.

Physical and Emotional Health of Gulf War Veteran Women (Federally Funded)

Pierce (1997) administered questionnaires on physical and emotional health to 525 women who had been in the US Air Force at the time of the Gulf War. The veterans were from a selected cohort of 638 of whom 82% (525) were located. The questionnaire was sent to these participants at two different time points: 2 years after the Gulf War and then 2 years later. Of the sampled veterans 92% (484) returned the questionnaire at time 1 and 87% returned the questionnaire at time 2. Approximately one-third of the respondents had been deployed to the Gulf War. The remainder had been deployed elsewhere (veterans who were not deployed outside the U.S. during the time of the Gulf War were excluded). The researcher stratified on service status at the time of the War (Active Duty v. Reserve v. National Guard). Among the deployed veterans, Pierce (1997) stratified on duration in theater (<120 days v. >120 days).

Measures of general physical health were collected along with data on gender specific health problems such as gynecologic and reproductive health. On the general health questions respondents were asked to estimate the frequency with which symptoms were experienced in the previous 12 months. Measures of mental health included measures of anxiety, depression, and somatization. PTSD symptoms were also measured. The researcher also collected data on measures of role and emotional function, self esteem, and internal control orientation. Although the frequency of self-reported symptoms was generally higher in Gulf War deployed women veterans compared to their deployed-elsewhere counterparts, Pierce (1997) found no significant differences between deployed and non-deployed women veterans on self-reported measures of general health status at either time point. She did observe at time 1 that those veterans who served in the Gulf War less than 120 days self-reported more depression and insomnia compared to their non-deployed counterparts. Also at time 1, rash and unintentional weight loss were reported by women who served greater than 120 days compared to their non-deployed counterparts. At time 2 different results were observed from the questionnaire responses. Those women veterans who served less than 120 days self-reported more rash, cough, and memory problems than the deployed-elsewhere cohort. Those who served greater than 120 days also reported more cough compared to the deployed-elsewhere veterans. When data are aggregated the higher self-reporting of cough is not evident. It is not clear why there would be no difference in the reporting of cough among all deployed Gulf War veterans, when such differences are apparent in the time-stratified cohorts. Overall both deployed and deployed-elsewhere veterans reported, on the average, symptom frequencies between 1 and 2 occurrences in the past 12 months.

On gender-specific questions of health, at time 2 deployed veterans reported significantly more breast lumps or cysts, and abnormal pap smears, in comparison with their deployed-elsewhere counterparts. When stratified by time in theater, these differences were no longer apparent. Also, these differences did not appear at time 1.

With respect to measures of mental health, of the women deployed to the Gulf War 24% met diagnostic criteria for PTSD compared to 15% in the deployed-elsewhere cohort. The overall prevalence rate for deployed and deployed-elsewhere veterans was 18%. This is considerably higher than has been suggested from similar studies of mostly male Gulf War veterans. On other measures of mental health status there appears to be little difference between Gulf War deployed women veterans and deployed-elsewhere veterans.

The importance and strength of this study is that it is the first to report on the health of women Gulf War veterans, including both general and gender-specific health outcomes. A weakness of the study relates to the problem of multiple comparisons among a large number of outcomes. It is not clear that the researcher made any attempt to correct for this, and this diminishes the study's significance. Furthermore, the fact that Air Force veterans only were studied limits the generalizability of results to other veterans from other services.

Still, the gender-specific findings, as well as the PTSD findings from this study, are interesting. Several ongoing studies may be able

to shed additional light on these findings in the future.

Health Symptoms Reported by Persian Gulf War Veterans Two Years after Return (Federally Funded)

Researchers at the Boston VAMC and the White River Junction VAMC National PTSD Center have been following a cohort of more than 2,000 Army Gulf War veterans since their return from the Gulf in 1991. Within five days of their return psychosocial and family adjustment were assessed. At that time (Time 1) about 4% of these veterans had symptoms of PTSD (not different from background PTSD rates). Eighteen to twenty four months following Time 1 (Time 2), about 80% of the original cohort participated in a follow-up survey that also included more detailed questions on exposures in the Gulf and on health symptoms. Wolfe et al. (1998) report on findings from the Time 2 study in which they investigated possible associations between opportunities for exposure and increased rates of health symptom reporting.

Questionnaires that were administered to the cohort included the Mississippi Scale for Combat-related PTSD, general psychological well-being (Brief Symptom Inventory, BSI), Combat Exposure Scale (CES), and a 20-item Health Symptom Check List (HSC). They first examined descriptive data on types and rates of health symptoms reported by a cohort of Gulf War veterans. The mean number of symptoms endorsed by all participants was 2 (out of 20). Out of the entire cohort, 13% were categorized as having high symptom reporting (>5 symptoms), and 48% had no symptoms. To place these data in context, the researchers compared these results with symptom data acquired at the same time from a small cohort (n=38) of activated, but non-deployed veterans. The non-deployed group reported a mean of 0.82 symptoms, which was significantly lower than in the deployed group. The five most commonly endorsed symptoms were general aches/pains, lack of energy, headaches, insomnia, and feeling nervous and tense. To investigate the relationship between self-reported exposure and health outcome, investigators defined three dichotomous exposure variables: (1) high versus low combat exposure; (2) being in a transportation unit; and (3) self-reported exposure to chemical and/or biological warfare agents ("poison gas" and/or "germ warfare").

The researchers found that overall, PTSD symptomatology was associated with health symptom endorsement. A higher proportion of soldiers who reported high combat exposure or exposure to chemical and/or biological warfare agents had PTSD symptomatology. When the investigators examined the relationship between exposure and health symptom reporting they found that each of the three exposure variables was associated with increased rates of self-reported health problems. After adjusting for demographic, lifestyle, and psychological stress characteristics, those subjects describing exposure to chemical and/or biological warfare agents were still at increased risk for reporting health symptoms. When persons with presumptive PTSD were excluded from the analysis, self-reported exposure to chemical/or biological warfare agents continued to be predictive of increased health symptom reporting. These findings suggest that self-reported exposure to chemical and/or biological warfare agents is related to higher symptom reporting by this cohort of veterans.

A strength of this study is the large number of subjects studied. However, the group itself is not necessarily representative of all Gulf War veterans. In addition, the study is limited by recall bias for self-reported exposure. In fact many participants changed their answers on exposure to chemical or biological warfare agents from time 1 to time 2. The researchers speculate that reported or perceived exposure to chemical or biological warfare agents could represent a unique combination of many factors including attributions regarding the health effects of hazardous exposure, perceived associations between health and hazardous substances, and demonstrated links between health and subsequent psychological stress.

A Survey of Outpatient Visits in a United States Army Forward Unit during the Gulf War (Other DoD Funding)

Wasserman et al. (1997) report on a review of surveillance data on outpatient visits between October 1990 and March 1991 from the 3rd Armored Cavalry Regiment. During that time a total of 6,772 sick call visits were recorded at four squadron aid stations, the regimental headquarters aid station, and the clearing station. Over 90% of the visits were to the squadron aid stations or the clearing station.

The investigators found that nontraumatic orthopedic problems accounted for the highest incidence of primary health care visits, followed by unintended injuries, and gastrointestinal, respiratory, and dermatologic conditions. Visits for heat injuries, sexually transmitted diseases, unexplained fever, and psychiatric problems were low, probably due to preventive measures. Overall the health of the troops in the 3rd Armored Cavalry Regiment was very good.

The investigators conclude that increased prevention to decrease orthopedic problems and unintended injuries may substantially reduce outpatient visits during future deployments. They also point out that medical surveillance during future deployments can be improved by taking advantage of current advances in technology to facilitate patient data retrieval and provide timely information to first- and second-echelon medical personnel.

The results of this study apply to only one regiment among all troops deployed to the Gulf War. It cannot be used to make any general conclusions about the health of the entire Gulf War troop population during deployment. However, this study demonstrates the importance and value of an active health surveillance program for all troops during deployment.

B. Presentations and Poster Sessions at National Scientific Conferences Related to Illnesses in Gulf War Veterans

National and international meetings of scientists are important venues for reporting and sharing new research results through poster and platform presentations to scientific colleagues. Often the research results represent works in progress and do not represent final results. Furthermore, the content of the presentations have not been subjected to external scientific peer-review. Thus, when discussing results of presentations at scientific meetings great care must be taken in weighing these results in comparison with results published in the peer-reviewed literature. In most cases, the research presented at national meetings is later published in peer-reviewed journals, but it is also likely that by that time they will have undergone considerable changes as a result of the critical scrutiny of scientific peers.

With this caveat in mind, summaries of presentations presented at two major scientific meetings held this year are presented below. Abstracts of the presentations are in Appendix B.

1. American Psychological Association, Chicago, August 15-19, 1997

As a part of the annual meeting of the American Psychological Association in Chicago, a special symposium was held on August 16: "Persian Gulf War Veterans Health Complaints: Psychological Studies". This symposium focused on research on psychological outcomes being conducted at each of the three VA environmental hazards research centers (EHRC).

The emphasis of the Portland EHRC presentations was on the use of easily administered, automated testing for assessments and the predictive value of test instruments being used in identifying Gulf War veterans with unexplained illnesses. The East Orange EHRC presentations focused on their research on fatiguing illnesses and the occurrence of psychiatric disorders in their sample of Gulf War veterans from the VA Persian Gulf Registry. The Boston EHRC presentations contrasted findings on self-reported symptoms and on neuropsychological test findings in Gulf War veterans and veterans deployed to Germany during the Gulf War.

2. American Public Health Association, Indianapolis, November 10-11, 1997

The annual national conference of the American Public Health Association was held in Indianapolis from November 9 to 13, 1997. Researchers delivered 27 oral or poster presentations that were directly relevant to illnesses in Gulf War veterans. Of these, 19 were reports of research results and 2 were reports of clinical follow-up or evaluation. Most of these have not been published or presented publicly before. Six of the presentations were on policy issues.

C. Summary of New Research Information

1. Brain & Nervous System

In the past year a number of studies examining outcomes related to the brain and nervous system in Gulf War veterans have been published.

Several studies have variously examined neuropsychological, psychological, and symptom outcomes, and their interrelationships. Studies by Axelrod et al. (1997) and Hom et al. (1997) indicate that Gulf War veterans with altered neuropsychological function have more psychological problems as well. It is not, however, clear that these findings demonstrate a causal association between these outcomes. However, Proctor et al. (1997) reported at the Annual Meeting of the American Public Health Association that a group of deployed Gulf War veterans had more neurocognitive problems (mood, verbal memory, and visual memory) than a group of veterans who had been deployed to Germany at the same time. These cognition problems could not be explained by any concurrent psychological problem.

Wolfe et al. (1998) and Baker et al. (1997) have reported that Gulf War veterans with PTSD symptomatology also report more somatic complaints such as fatigue, nausea, muscle aches, etc.

At the 1997 Annual Meeting of the American Psychological Association, Lange et al. (1997) and Fiedler et al. (1997) reported on East Orange VA Environmental Hazards studies of VA Persian Gulf Registry Veterans. They found that about 50% of those with fatiguing illness had two or more psychiatric diagnoses. However, of the remaining 50%, more than half had no psychiatric diagnosis. Furthermore, the ratio of those who had one psychiatric diagnosis to those who had none was similar to a healthy control group with no fatiguing illnesses. In a logistic regression, Fiedler et al. (1997) found that the personality trait of negative affect and self-reported exposures were significant predictors of case status (i.e., fatiguing illness, with and without concurrent psychiatric disorders). Thus, the studies suggest that psychological distress may not be able to account for fatiguing symptoms in as much as 50% of symptomatic veterans.

In another presentation at the American Psychological Association, preliminary results on neuropsychological testing of the same Registry participants at East Orange indicate that veterans with fatiguing illnesses tend to have problems with rapid information processing, which is common in civilians with Chronic Fatigue Syndrome. However, the Registry participants with fatiguing illnesses also have problems in abstract thinking and organizing thoughts effectively (Lange et al., 1997).

Overall, research to date suggests that psychological distress alone cannot explain all symptoms reported by Gulf War veterans.

There have been new advances in PTSD research in Gulf War veterans that may lead to improved understanding of the disorder and better ways to prevent and diagnose PTSD. Research by Vasterling et al. (1997) suggests that intellectual resources may play an important role in buffering an individual against the psychopathology that can follow stressful exposures. Vasterling et al. (1998) have also shown that intrusion of traumatic memories may be part of a more general pattern of disinhibition (the inability to prevent intrusive memories) going beyond trauma-related cognition. Lastly, Southwick et al. (1997) found evidence that PTSD may lead to the amplification and distortion of recalled traumatic events and thereby create a quandry in the diagnosis of PTSD because it heavily relies upon the accuracy of recall.

2. Chemical Warfare

Gray et al. (1997) reported preliminary results of a sub-study of their larger published study of military hospitalizations (Gray et al., 1996). They examined records of hospitalizations in military treatment facilities between 1991 and 1995 for troops identified as being under the sarin plume which may have resulted from the demolition of the Khamisiyah, Iraq, weapons depot in March, 1991. They compared hospitalization data between the troops under the plume and troops identified as being outside of the plume footprint. Preliminary results indicate no difference between these two groups in the rate of hospitalization in military treatment facilities between 1991-1995. Although this study has methodological limitations, it is the first study that compares health measures between troops possibly exposed to low levels of sarin with those whose exposure was very unlikely.

Three important human studies have been published in the past year that relate to the sarin terrorist incidents in Matsumoto, Japan in 1994, and in Tokyo in 1995.

Follow-up of acutely symptomatic victims of Tokyo sarin incident 6-8 months following exposure show that they experience more psychiatric symptoms and fatigue which appear to be associated with a diagnosis of PTSD rather than directly related to sarin exposure (Yokoyama et al., 1998a). However, PTSD does not explain the findings of asymptomatic neurological sequelae. Brain electrophysiologic studies show that in some currently asymptomatic victims, there appear to be subtle deficits in the higher cortical and visual nervous systems (Murata et al., 1997). In addition a study of balance in these subjects (Yokoyama et al., 1998b) suggests a potential effect on the vestibulo-cerebellar system that is dose-dependent with respect to the acute AChE activity levels.

In a 2 year clinical follow-up of victims of the Matsumoto sarin terrorist incident (Sekijima et al., 1997), severely poisoned victims (those with a reduction in cholinesterase levels greater than 75%) continue to have clinically measurable sequelae such as epileptic encephalographic changes, fever, hypoxia, and cardiac arrhythmia . However, for those who were moderately (cholinesterase reduction of 0% to 75%) or mildly exposed (no cholinesterase reduction, but acutely symptomatic with miosis at the time of exposure) clinical abnormalities did not persist. These studies suggest that exposures resulting in acutely symptomatic responses may lead to persistent chronic effects that vary in a dose-dependent fashion. These effects vary from clinically undetectable (but apparent upon sensitive neurological testing) to clinically significant with overt signs and symptoms. These effects may not be related to the acutely toxic effects of cholinesterase reductions.

The significance of these findings is underscored by a study in rats (Prendergast et al., 1997) that shows that chronic exposure to DFP (a ChE inhibitor) impairs spatial learning even after ChE levels have returned to control levels 21 days following cessation of a 14 day DFP exposure.

The overall significance and relevance of the Japanese studies and the rat study to Gulf War veterans is uncertain because in all of the studies acute signs of poisoning at the time of exposure were evident. They do indicate the potential for long-term central nervous system effects following exposure to a cholinesterase inhibitor.

Lastly, an important advance has been made in the area of biomonitoring for nerve agent exposure. Polhuijs et al. (1997) report on the ability to reactivate butyrylcholinesterase, thereby releasing measurable quantities of sarin in the sera of victims of the Tokyo and Matsumoto incidents. These findings may have important implications for direct measurements of sarin exposure.

3. Depleted Uranium

At the 1997 Annual Meeting of the American Public Health Association, McDiarmid et al. (1997) reported on their clinical follow-up study of 33 individuals with embedded depleted uranium fragments. To date they have found no evidence of any renal damage nor any other long-term sequelae.

4. Mortality

At the 1997 Annual Meeting of the American Public Health Association, Kang et al. (1997a) reported on the expanded VA mortality study. The prior study (Kang et al., 1996) showed no disease-specific causes of excess mortality in Gulf War veterans studied through September, 1993. In the present study they extended the study period through December 1995. As with the original study, preliminary evidence from the current study does not show any excess disease-specific mortality in Gulf War veterans.

In both the original and expanded studies of Kang et al. (1996, 1997a) the investigators found excess deaths due to external (not disease-related) causes, in particular motor vehicle accidents. Kang et al. (1997b) also reported on an attempt to ascertain risk factors for excess motor vehicle deaths among Gulf War veterans. A preliminary analysis of records from the Department of Transportation shows that prior to fatal motor vehicle accidents involving Gulf War veterans, behavioral factors such as driving over the speed limit and non-use of seatbelts may be associated with increased deaths.

5. Reproductive Health

Two important population-based studies on birth defects were published in the past year. The first one reported by Cowan et al. (1997) was a study of live births at 135 military medical facilities in 1991, 1992, and 1993 (33,998 of deployed vets, 41,463 of non-deployed vets).

The investigators found no difference in the number of overall birth defects in Gulf War veterans' offspring compared to the offspring of non-deployed veterans.

A sub-study of the research reported above (Araneta et al., 1997) showed that there was no statistically significant difference between Goldenhar Syndrome (an oculo-auriculo-vertebral defect) in the newborn infants of deployed veterans compared to the infants of non-deployed veterans. However, since the number of case infants was few, and the sampled population was small for a rare birth defect, these results must be interpreted with caution. Furthermore, chance could not be excluded as an explanation for these findings.

The cause of Goldenhar Syndrome in the general population has not been clearly elucidated. In the present study, all 7 case infants had fathers who served in the military. At this time paternal exposure has yet to be clearly established as a cause of birth defects, in general.

6. Symptoms/General Health

A number of researchers are adding to the body of epidemiologic research on symptoms and general health conditions in Gulf War veterans.

Researchers at the Portland VA EHRC (PEHRC) reported on findings from their population-based survey of Gulf War veterans that raise concerns over the validity and reliability of self-reported exposures and symptoms. McCauley et al. (1997) reported that rates of self-reported symptoms declined in a cohort of 154 veterans who reported unexplained symptoms from the time of their original mail survey, to a follow-up telephone survey, to the final clinical examination. Spencer et al. (1997) provided preliminary data on self-reported exposures among 108 Gulf War veterans (from a randomly selected cohort) who were only in the Persian Gulf either before or after Operation Desert Storm, but not during it. Among these subjects there were self-reports of exposures that were not likely to have occurred during Operation Desert Storm. Test-retest reliability for 21 exposures listed on their questionnaire was excellent for only one self-reported exposure - distribution of PB tablets. Both of these studies point out the importance of objective measures of both exposure and health outcome in these kinds of epidemiologic investigations.

Doebbeling et al. (1997) provided a preliminary report on additional analyses of results from the Iowa study of Gulf War veterans (Iowa Study Group, 1997). They performed factor analysis on the answers to 137 symptom questions from the original telephone survey of Iowa Gulf War veterans and non-deployed era veterans. The symptoms grouped into three factors each encompassing multiple symptoms. The investigators named the factors "somatic", "distress", and "panic" based on the types of symptoms that clustered together. The important aspect of this analysis is that it was applied separately to both the deployed and non-deployed study cohorts. Preliminary findings indicate no difference in the pattern of clustering between these two groups. This suggests that although the deployed veterans reported more symptoms overall than their non-deployed counterparts, the pattern of symptom reporting did not differ and was, therefore, not suggestive of a unique "syndrome".

Pierce (1997) has published the first results of a study focusing on health outcomes in women Gulf War veterans. She conducted a health survey 2 and 4 years following the Gulf War of women in the Air Force at that time. The researcher found that at 4 years following deployment some gender-specific health problems were self-reported more frequently among the deployed versus the deployed-elsewhere cohort. Unfortunately, the lack of physical examinations to confirm these self-reports is a limitation of the study. PTSD was also found to be more prevalent among the deployed compared to the deployed-elsewhere veterans. Notably the overall rates of PTSD appeared to be high in both deployed and deployed-elsewhere women veterans in comparison with results from other studies of Gulf War veterans primarily involving men.

7. Other

At the APHA meeting, Knoke et al. (1997) reported preliminary data on testicular cancer diagnosed in military treatment facilities between 1991 and 1995. They found no difference in the reporting of testicular cancer in DoD-hospitalized Gulf War veterans compared to their non-deployed counterparts.

III. RESEARCH FUNDING TRENDS

1. Overview

Appendix A comprises the current contents of the Gulf War Veterans' Research Database. This database was last updated during the first quarter of FY'98. Research projects are grouped according to the Department that is responsible for the conduct or sponsorship of the research.

Each entry in the database includes:

- Project Title
- Responsible Federal Agency
- Study Location
- Project Start-up Date
- Project Completion Date (estimated if ongoing)
- Overall Objectives of Project
- Specific Aims of Project
- Methods of Approach
- Expected Products (Milestones)
- Current Status/Results
- Publications

Two descriptors can approximately categorize each research project. The first descriptor is a series of **research focus areas**. These are research areas that have been defined as being particularly important. The current areas of research focus are categorized as follows:

- Prevalence and risk factors for symptoms and alterations in general health status
- Brain and nervous system function
- Chemical weapons
- Environmental toxicology (e.g. studies focused on specific environmental toxicants such as pesticides, oil well fires, etc.)
- Reproductive health
- Depleted uranium
- Leishmaniasis
- Immune function
- Pyridostigmine bromide
- Mortality experience
- Interactions of exposures (chemical, environmental, biological, pharmacological, etc.)
- Prevention of diseases and illnesses (i.e. studies that will produce knowledge that could inform disease and illness prevention strategies.)
- Treatment
- Diagnosis (i.e. studies that will improve the ability to diagnosis previously undiagnosed conditions, or to better refine diagnoses with new tools applied to existing definitions.)

The number of focus areas has expanded since last year by the addition of the new focus areas: *Interactions, Prevention, Treatment, and Diagnosis.* Each project is assigned up to three focus areas as categorical descriptors. This allows accounting for projects that cover multiple focus areas. For example, a project on the neurophysiological effects of exposure to sarin in animals would have a focus on the brain and nervous system, and a focus on chemical weapons. The number of focus areas (between one and three) assigned to a project depends on the project itself.

The other descriptor for each project is **research type**. Each research project uses a method of approach to test a specific research hypothesis. Approaches range in type from basic research, addressing potential biological mechanisms of causation, to clinical and epidemiological research that attempts to ascertain illness prevalence and risk factors. Although precise categorization of research types can be difficult because of overlapping methodologies, Gulf War veterans' illnesses research projects can be divided into the following general types:

BASIC RESEARCH: research into mechanisms of disease using *in vitro* and *in vivo* models of human disease.

CLINICAL RESEARCH: application of an intervention, such as in a controlled drug trial, or use of methodologies such as case-control studies to define disease risk factors.

EPIDEMIOLOGY RESEARCH: includes population-based studies focused on outcomes such as mortality, symptoms, hospitalizations, etc., using devices such as postal surveys, telephone interviews, and records reviews.

VACCINE AND DRUG DEVELOPMENT: application of known scientific principles to the development of biologically based prevention, intervention, and treatment measures.

The Gulf War Veterans' Illnesses Research Database catalogs only research that either directly involves Gulf War veterans, or has been initiated to answer specific questions about risk factors. A case of the latter is a research project using animal models for low-level chemical warfare agent health effects. The database does not account for the vast accumulated knowledge derived from the nation's investment in biomedical research over the past 40 years.

Lastly, the Gulf War Veterans' Research Database only contains research that is federally sponsored. This includes research conducted by federal scientists, as well as that by non-federal scientists supported by federal research funds through grants and contracts. It is not possible to ensure that all research efforts are tracked that fall within the private sector or otherwise outside of the purview of the Federal Government. Notwithstanding, the Research Working Group attempts to stay abreast of all research relevant to Gulf War veterans' illnesses. The Research Working Group accomplishes this by monitoring the peer reviewed published scientific literature, attending scientific meetings, and even using newspaper reports and personal accounts of researchers.

Regardless of the entity that supports particular research projects, <u>all</u> research that has undergone rigorous peer review and has been published in peer reviewed scientific literature will ultimately be used in formal assessments of the nature and cause(s) of Gulf War veterans' illnesses.

The next sections will provide a quantitative overview of the current research portfolio on Gulf War veterans' illnesses and the evolution of the portfolio over time since 1994. Topics that will be covered include overall research expenditures from 1994-1998 (projected), and the types and areas of research in which the Federal Government has invested.

2. Research Funding

Virtually all current federal research projects directly related to Gulf War veterans' illnesses are sponsored by VA, DOD, or HHS. From 1994 through the present, the Departments have sponsored 121 distinct research projects on Gulf War veterans' illnesses. This does not include research projects that recently have been selected for funding but are currently in final negotiations. Nor does it account for anticipated projects arising from upcoming competition of proposals submitted in response to new initiatives, such as the DoD/VA initiative on the neurobiology of stress.

The scope of the federal research portfolio is broad. In size, projects range from small pilot studies utilizing limited or no direct appropriated research funds, up to large-scale epidemiology studies and major research center programs utilizing significant amounts of appropriated research funds.

A table in Appendix A lists all of the research projects and programs supported now or in the past by the Federal Government. The appropriated funds centrally distributed to each program or project are shown in the fiscal years that funds were obligated. Many extramural projects are multi-year efforts for which funds are obligated at the beginning of the project period. An entry of $0 is placed in the fiscal year column for each project for years in which funds were not obligated, but the project was ongoing. Blank entries for a project in any given fiscal year indicate a period of no research activity (years before a project was initiated, or years after a project was completed).

Table III-1 is a summary of research expenditures by DoD, VA, and HHS between FY'94 and FY'97, and a projection of funding into FY'98. Currently, the Federal Government is projecting cumulative expenditures of $115.2 million for research from FY'94 through FY'98.

Table III-1. Funding for Research FY'94-FY'98

Department	*FY'94*	*FY'95*	*FY'96*	*FY'97*	**FY'94-97**	**FY'98**
DoD	$5.9	$12.5	$12.3	$31.8	**$62.5**	**$20.2**
VA	$1.2	$2.3	$4.9	$2.4	**$10.8**	**$16.5**
HHS		$2.5	$1.6		**$4.1**	**$1.2**
Total	$7.1	$17.3	$18.8	$34.2	**$77.4**	**$37.9**

Through February 1998, 39 projects have been completed, 78 projects are ongoing and 4 projects that have been awarded funds are pending. Table III-2 is a year by year account of completed projects and new projects.

Table III-2 Number of New and Completed Projects by Year

Fiscal Year	*New*	*Completed*
1994	20	3
1995	33	8
1996	22	4
1997	14	15
1998	14**	21*

*Projected for all of FY'98
**Does not include projects starting after 3/1/98 nor projects under final negotiation

3. Diversity of Research Approaches

The funds that have been invested in research on Gulf War veterans' illnesses over the years have gone into a broad-based portfolio with respect to research type and research focus area. Figure III-1 illustrates the number of projects of each research type for each year since FY'94. On the average epidemiology and clinical research have each comprised approximately about one third of the total number of projects. The remaining third has been divided between basic and vaccine and drug development with the larger share going to basic. However, as the number of clinical and basic research projects has increased over time, the number of epidemiology projects has begun to stabilize. As a fraction of the overall research portfolio, the number of epidemiology projects has fallen by about 10% since 1994. This reflects a decreased need for additional studies of symptoms and illnesses as the ongoing studies begin to provide results.

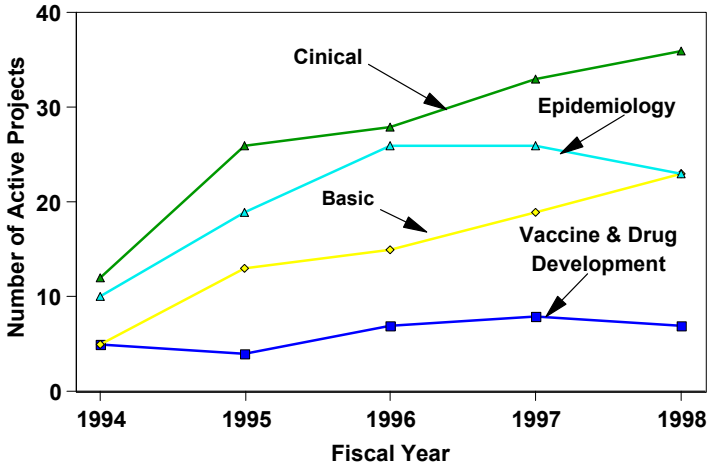

Figure III-1. Number of active research projects of different types for each fiscal year

The investment of funds across different research focus areas is illustrated in Figure III-2. Projects for each focus area are included based on whether the focus area is listed as one of the three focus areas assigned to each project. The total funds invested by research focus areas are shown in Figure III-2 in two ways. For each focus area, a black bar represents the total funds invested in all projects that have that focus area listed as being primary. A clear bar represents the total investment in projects where the focus area is listed as being secondary or tertiary. Thus the total height of a bar represents the investment for all projects for which the focus area is listed as primary, secondary, or tertiary. By showing the data this way the multiplicative effects of research investments are demonstrated. A project that examines Brain and Nervous System outcomes as a result of Pyridostigmine use is, therefore, counted under both of these focus areas.

prevalence of symptoms and illnesses in Gulf War veterans, and the focus of clinical research efforts on risk factors for illnesses. The focus on the brain and nervous system is a result of both the dominance of health complaints in this area, and the fact that many of the potential exposures in the Gulf were to neurotoxins. The third largest investment in research is in the focus area of Diagnosis. This is a natural outcome of the research centered on characterizing Gulf War veterans' illnesses, and on specific diagnostic tests such as the research on a serological assay for leishmaniasis.

The number of research projects in the various research focus areas has changed over time since 1994 as a reflection of the evolution of issues centered on Gulf War veterans' illnesses. Of note is a relatively greater increase over the years of research on chemical interactions, chemical warfare agents and pyridostigmine bromide. These increases are an

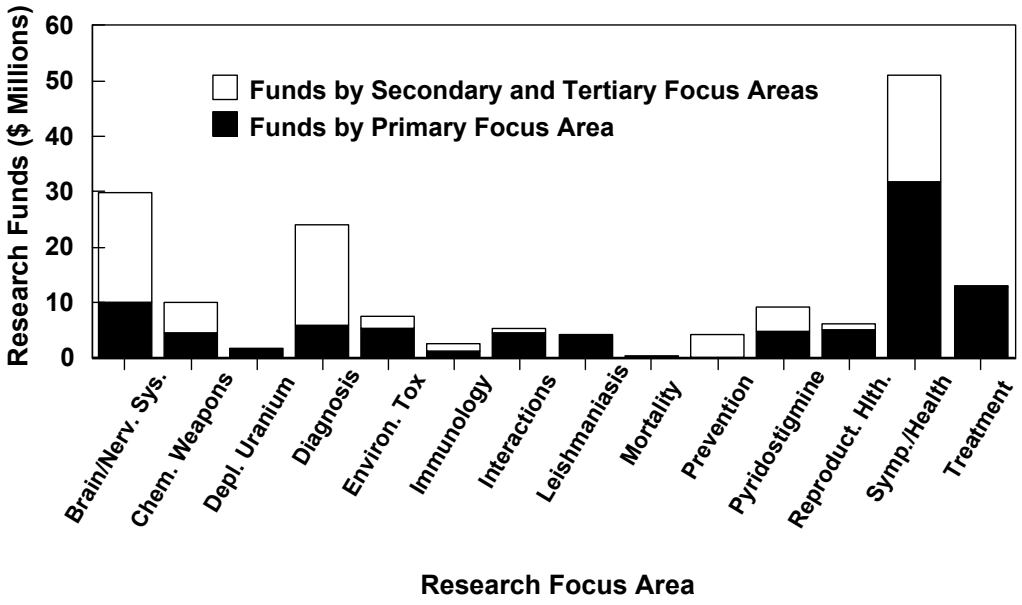

Figure III-2. Research costs by research focus areas

As can be seen in Figure III-2 the overall investment of funds has been greatest in the focus areas of the Brain and Nervous System and in Symptoms and General Health. This reflects the focus of epidemiological efforts on the outgrowth of increased concern over the health risks posed to veterans by exposures to multiple toxic agents at low-levels.

4. Government and Non-Government Researchers

Research sponsored by the Federal Government is conducted at a variety of institutions and laboratories inside and outside of government. It has been important to the government to have a research portfolio that taps into the widest range of intellectual resources. Of the 121 projects that the government has sponsored over the years, 48 have been conducted at sites that almost exclusively involve government researchers. Many of these projects have taken advantage of resources unique to the Federal Government and would have been difficult to carry out by the non-government sector. An example includes the outstanding in-house expertise the Walter Reed Army Institute of Research has in the area of leishmaniasis research. Another is ready access to large military health and demographic databases. Non-government scientists, located primarily at universities, have been conducting twenty-seven of the projects. The remaining 46 projects have involved government and non-government consortia of institutions and researchers. Examples include the VA Environmental Hazards Research Centers which entail close collaborations between VA medical center clinician/researchers and scientists at each VAMC's affiliated university. Government/academic/private collaborations have been an invaluable asset to the research program because they combine the strengths of government and non-government laboratories and scientists. They also lead to outside ideas and approaches, and provide the government with objective and independent input into its research efforts.

IV. NEW RESEARCH PROJECTS, INITIATIVES, AND MILESTONES

Besides new research findings appearing in the scientific literature and at national meetings, there have been several important events since the Report to Congress for 1996 that deserve discussion. These include the awarding of new research projects and the development of new research initiatives including solicitations for new research.

Many of the new research projects and initiatives are the direct result of recommendations from a variety of sources including the Presidential Advisory Committee on Gulf War Veterans' Illnesses (PAC, 1996b), the Institute of Medicine Panel on the Health Consequences of Service in the Persian Gulf War (IOM, 1996), and the RWG (PGVCB, 1995, 1996b)

A. New Research Projects

1. New Research Projects from DoD Broad Agency Announcement

In June 1995 DoD issued a Broad Agency Announcement (BAA) for additional research to fill research gaps identified at the end of the original *A Working Plan for Research on Persian Gulf Veterans' Illnesses* (PGVCB, 1995). Fourteen new research projects were selected and funded in the summer of 1996. These new projects were reported in the Annual Report to Congress for 1996 (PGVCB, 1997b). They covered the focus areas of:

Symptoms/General Health

Brain and Nervous System

Reproductive Health

Pyridostigmine Bromide

Environmental Toxicology

Leishmaniasis

Following the announcement by DoD in June 1996 that U.S. troops blew up a weapons bunker containing chemical warfare nerve agent at Khamisiyah, Iraq, the Research Working Group developed a two pronged approach to reorienting the research agenda in accordance with new information. This approach involved an immediate, short-term response and a more forward-looking long-term response. The short-term response was reported in the *1996 Annual Report to Congress*.

The recommended long-term response to the events at Khamisiyah that was developed involved soliciting new research projects in the following areas:

- Feasibility of epidemiological studies, including assessment of appropriate design and methodological considerations to assess the possible health effects of low-level, including sub-clinical, exposures to chemical weapons agents; and

- Additional applied toxicological or clinical studies designed to assess the pathophysiological effects of low-level, including sub-clinical, exposure to chemical warfare agents.

The recommendation to solicit new research on chemical warfare agents, along with other recommendations contained in the 1996 update of the *Working Plan* for research (PGVCB, 1996b), led to the release of a DoD Broad Agency Announcement (BAA) for new research. The RWG worked with the staff of the US Army Medical Research and Materiel Command in late 1996 and early 1997 to develop a BAA that encompassed four areas of research divided into three separate rounds of scientific and programmatic reviews. The final revised BAA covering these four areas was published in Commerce and Business Daily in January 1997 (Appendix C1). The four areas of interest were: (1) feasibility studies for conducting epidemiological research on the health of Gulf War veterans at Khamisiyah during the first two weeks of March 1991; (2) animal studies of the toxicological effects of low-level, sub-clinical exposures to chemical warfare nerve agents; (3) investigations of causal relationships between Gulf War veterans' illnesses and a variety of different potential exposures; and (4) studies of historical war syndromes, including potential causative factors. The first two areas were included in the first round of submissions, and the last two comprised the second and third rounds respectively.

A total of 71 proposals were submitted in response to the DoD BAA. Expert panels selected and managed by the American Institute of Biological Sciences under contract to the US Army Medical Research and Materiel Command carried out scientific reviews of submissions.

After the expert panels assigned scientific merit ratings, a subcommittee of the RWG provided secondary reviews for relevance as described in Sec. II.C of this report. The subcommittee developed a list of projects it would recommend for funding to DoD. Upon concurrence by the Chair of the RWG, these recommendations were transmitted to the Army, which then initiated negotiations with the Principal Investigators of the recommended projects. Given the funds set aside for rounds one and two, awards of 12 new projects from the first two rounds were made. These were announced in the fall of 1997. Awards from the third round are expected by mid-1998. Residual funds from the third round were used to fund additional research projects from the first two rounds that were judged scientifically meritorious but for which sufficient funds were not available. These projects will also be announced by mid-1998.

Brief summaries of the 12 newly awarded projects from the first two BAA rounds are provided in Table IV-1.

2. New Centers for Disease Control and Prevention Cooperative Agreements

In spring 1997, CDC issued a call for proposals to establish up to two cooperative agreements with academic institutions, funded up to $600,000 each for up to three years. (The solicitation is in Appendix C2.) The purpose of this initiative is to investigate clinical correlates of self-reported symptoms and illnesses in Gulf War veterans, and to characterize Gulf War veterans' illnesses in ways that will potentially produce medically sound case definitions. Proposals were submitted to CDC for review by an outside peer review panel. As with the BAA submissions, the RWG provided secondary programmatic reviews of the CDC submissions. Two cooperative agreements funded. These projects are described below.

Cognitive Function and Symptom Patterns in Gulf War Veterans -- Boston University School of Public Health (HHS-5)

This study will use functional magnetic resonance imaging (fMRI) to determine if there are differences in patterns of brain activation among Gulf War veterans reporting a high level of physical symptoms, Gulf War veterans with fewer symptoms, and veterans deployed to Germany at the same time. In addition, researchers will conduct an assessment of the relationship between brain activation patterns and levels of cognitive functioning. Patterns of activation on fMRI will be measured while the subject is presented with a number of challenge paradigms including a finger tapping task and a test of visual working memory.

The investigators will also use a mathematical technique known as Logical Analysis of Data (LAD) to examine previously collected symptom data from the Gulf War and Germany-deployed veterans. They will analyze the data to determine if there is a set of complaints characteristic of Gulf War service that could be useful for determining etiology or developing a case definition.

Neuropsychological tests and symptom prevalence measures will be replicated in a group of Gulf War deployed Danish veterans and in a group of non-deployed Danish veterans.

Defining Gulf War Illness -- University of Medicine and Dentistry of New Jersey-Robert Wood Johnson Medical School (HHS-6)

The purpose of this study is to characterize and compare alternative classifications for symptoms and functional disability that remain medically unexplained in Gulf War veterans. This will be accomplished in three phases. Phase I will assess persistence and stability of symptoms over time, as well as compare the performance of data-driven case definitions derived from two samples: 1) the New Jersey Center for Environmental Hazards Research sample of Gulf War veterans participating in the Department of Veterans Affairs Gulf War Registry; and 2) a cohort of Air Force members from a previous CDC study of Gulf War veterans and Gulf War-era controls from Pennsylvania and Florida. In addition to assessing data-driven case definitions for illness among Gulf War veterans, existing definitions for medically

(Continued on Page 35)

TABLE IV-1
NEWLY AWARDED PROJECTS FROM 1997 DOD
BROAD AGENCY ANNOUNCEMENT

Project #	Title	Principal Investigator	Institution	Total Budget	Est. Comp. Date	Summary
DoD-53	Long-Term Effects of Subclinical Exposures to Sarin	Rogene F. Henderson, Ph.D.	Lovelace Respiratory Research Institute, Albuquerque, NM	$1,000,000	2/29/00	This study will examine nervous system effects of low level sarin delivered by inhalation to rats. This study will explore the possibility of long-term effects from short-term subclinical exposures to sarin by Gulf War veterans.
D0D-54	Assessment of Subchronic Neurobehavioral and Neuropathologic Effects in Rats Following Low-Level Sarin Exposures	Carl T. Olson, Ph.D.	Battelle, Columbus, OH	$414,375	10/30/99	This study will assess brain and behavior effects of low-level sarin exposure in rats, with or without combinations of insect repellent and pesticide. This may help to explain symptoms in Gulf War veterans caused by a specific combination of chemical exposures.
DoD-55	Low-level exposure to GB vapor in air: diagnosis/dosimetry, lowest observable effect levels, performance-incapacitation, and possible delayed effects	Herman Van Helden, Ph.D.	TNO Prins Maurits Laboratory, Netherlands	$630,013	10/29/00	This study will assess effects of sarin and possible interactions with pyridostigmine bromide in guinea pigs and marmoset monkeys, using doses of sarin which do not produce visible signs of exposure.
DoD-56	Low-Level Sarin Neurotoxicity and Its Modulation by Pyridostigmine	Barry Wilson, Ph.D.	University of California, Davis, California	$785,000	02/28/01	This study will study interactions of low-level sarin and pyridostigmine bromide in hen and mouse models to determine if pyridostigmine bromide provides any protective effect on the nervous system.

TABLE IV-1 (Cont.)

Project #	Title	Principal Investigator	Institution	Total Budget	Est. Comp. Date	Summary
DoD-57	Physiologic Effects of Stress in Gulf War Veterans	Daniel Clauw, M.D.	Georgetown University, Washington DC	$908,620	10/29/00	This project will test the hypothesis that autonomic and neuroendocrine functioning in veterans suffering from undefined illnesses is similar to that of patients with fibromyalgia and chronic fatigue syndrome. Categorizing the physiological stress responses of Gulf War veterans will help to define Gulf War veterans' illnesses.
DoD-58	Illness Among Persian Gulf War Veterans: Case Validation Studies	Bradley N. Doebbeling, M.D.	The University of Iowa, Iowa City, IA	$2,207,635	10/24/01	This builds on a previous study of reporting of symptoms and illnesses in Gulf War veterans. This study will assess the prevalence of depression and cognitive dysfunction in Gulf War veterans. This helps to establish the magnitude of health problems in veterans.
DoD-59	Pyridostigmine-induced Neurodegeneration: Role of Neuronal Apoptosis	Gary E. Isom, Ph.D.	Purdue University, West Lafayette, Indiana	$616,975	10/24/00	This project will investigate the circumstances in which pyridostigmine bromide could have toxic effects and produce neurodegeneration in rodent models. This may help to explain some of the symptoms of memory loss and other neurological impairments reported by some Gulf War veterans.

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TABLE IV-1 (Cont.)

Project #	Title	Principal Investigator	Institution	Total Budget	Est. Comp. Date	Summary
DoD-64	Individual Differences in Neurobehavioral Effects of Pyridostigmine	Mary R. Cook, Ph.D.	Midwest Research Institute, Kansas City, MO	$1,899,523	02/29/01	This project will assess the individual variability to brain effects of pyridostigmine bromide in normal and dry heat conditions. This may help to explain why the incidence of side effects attributed to pyridostigmine bromide may have been higher during the Gulf War than in peacetime studies.

(Continued from Page 31)
unexplained symptoms, such as chronic fatigue syndrome, multiple chemical sensitivity, and fibromyalgia will be evaluated. Phase II will assess the generalizability of derived and existing case definitions in a random sample of deployed and non-deployed Gulf War era veterans. Phase III will involve assessment of psychiatric distress among Phase I and Phase II participants at risk for having a psychiatric diagnosis.

Funding for Health Assessments of Gulf War Veterans from Iowa (HHS-1 and DoD-58)

The CDC is extending funding for HHS-1. The original study was a telephone health survey of a population-based sample of deployed Gulf War veterans and non-deployed era veterans. The results of this study (The Iowa Persian Gulf Study Group, 1997) showed that Gulf War veterans are reporting more health symptom compared to their non-deployed counterparts. A limitation of the study was the self-reported nature of the symptoms and exposures.

CDC has extended this study to allow the performance of physical examinations on a sample of survey respondents in an attempt to correlate self-reported symptoms with more objective measures of asthma.

In addition, DoD has also funded Iowa investigators to use objective measures to assess the prevalence of depression and cognitive dysfunction in a subset of the original Iowa cohort (DoD-58). Both the CDC and DoD funded follow-up studies will complement Phase III of the VA National Survey of Gulf War Veterans which also involves a follow-up physical examination on previously surveyed Gulf War veterans (see section IV-B).

3. New Khamisiyah-Related Research

The events at Khamisiyah on March 10, 1991, and uncertainties about possible health outcomes associated with this event, led to two research pathways. The first was epidemiological research on health outcomes in troops potentially exposed to sarin at Khamisiyah. The second was more research focusing on the general topic of potential health consequences resulting from low, sub-clinical exposures to chemical warfare nerve agents alone and in combination with other exposures.

With respect to epidemiological research on potentially exposed cohorts at Khamisiyah, the RWG was concerned about its feasibility in light of the absence of quantitative exposure data. Plume dispersion models developed by DoD and CIA have helped to place upper bounds on exposure so that hazard assessments can be done.

Based on model-predicted exposure levels, troops were not located at sites where even mild acute health effects would be expected to have occurred. Indeed, no such effects were observed. However, if sound and reliable epidemiological research is to be conducted, quantitative exposure data, in particular exposure gradients, are needed to develop a sampling strategy and to determine the presence or absence of an exposure-response relationship. Because obtaining quantitative exposure data is very difficult (if not impossible), the use of plume model predictions, is necessary. However, the uncertainties associated with exposure models were compelling enough to suggest the need of a feasibility study. This led to one of the components of the first BAA round requesting such feasibility studies. Unfortunately, no investigators responded to the solicitation with a proposal.

DoD has contracted with the Medical Follow-up Agency (MFUA) of the Institute of Medicine (IOM) to develop an epidemiological protocol for Khamisiyah. The protocol was peer reviewed by the American Institute of Biological Sciences, and the RWG has recommended that DoD fund this study (DoD-69).

MFUA staff will ascertain morbidity and mortality outcomes in active duty and former active duty soldiers using passive records-based methods and compare the outcome rates among troops with varying likelihood exposure to chemical warfare agents. VA and DoD hospitalization and outpatient data will be used. Patterns of health perception and health care use will be compared before and after notification of possible chemical warfare agent exposure.

Other projects are also moving ahead in an attempt to answer some questions about whether exposure predicted by the modeled plume has resulted in any health problems among veterans. Databases that were developed to test broad hypotheses on mortality, DoD hospitalization rates, and birth outcomes in DoD hospitals for Gulf War veterans overall, are being examined for outcomes associated with Khamisiyah (Gray, 1997). In principle a subset of these large databases, defined by veterans who were under the modeled plume, can be queried about the specific outcomes of death, hospitalization, and adverse birth outcomes. These outcomes can be compared among veterans not under the plume, or non-deployed veterans. Exploratory protocols have been developed within DoD to conduct such database studies. Although they might not yield definitive findings, these efforts could stimulate the development of additional testable hypotheses.

Lastly, the 1997 BAA has added considerable new research on the potential for long-term effects of a variety of Gulf War risk factors including low-level exposure to nerve agents and the effects of interactions of neurotoxins (see Table IV-1).

4. Treatment Trials for Gulf War Veterans' Illnesses (VA/DoD – 1)

The Department of Veterans Affairs is undertaking two important research initiatives directly targeted at treatment of Gulf War veterans' illnesses. In the first initiative VA is leading a joint VA/ DoD project to develop a protocol for a multi-site (VA and DoD facilities) randomized treatment trial of Gulf War veterans with symptom complexes such as Chronic Fatigue Syndrome(CFS) and Fibromyalgia (FM). A Planning Committee composed of VA and DoD researchers will develop the protocol. When complete, the protocol will be submitted to a subcommittee of VA's Cooperative Studies Evaluation Committee (CSEC, a federally chartered committee) for expedited peer review. Start-up of this trial is anticipated for late calendar year 1998.

In the second initiative, VA has issued a Program Announcement to VA researchers for additional randomized, multi-site treatment trials for Gulf War veterans' illnesses (a copy of the Program Announcement is in Appendix C3). Interested researchers submit a planning request to conduct a multi-site trial. Each planning request will then undergo initial review by the VA Office of Research and Development Cooperative Studies Program. Depending on potential merit following internal review, the researcher may be invited to submit a fully developed protocol. The protocol will then undergo scientific peer-review by VA's federally chartered Cooperative Studies Evaluation Committee (CSEC). Further revisions and reviews of the protocol are made until final approval or rejection by CSEC.

5. Other New Research and Research-Related Initiatives

Neurobiology of Stress

The Final Report of the PAC (PAC, 1996b) recommended that additional research efforts be made in the area of stress and the neurobiology of stress. In 1997 VA and DoD issued a request for proposals (see Appendix C4) from intramural VA and DoD clinician/scientists for research on stress and stress-related disorders. The neurobiological aspects of stress are emphasized in this solicitation. Proposals were to be submitted by January 15, 1998. Proposals will undergo external scientific review by a joint VA/DoD appointed panel of experts, followed by programmatic review by the RWG. Award and funding of projects is expected by July 1, 1998.

Computerized Neuropsychological Test Battery

It can be difficult to discriminate patients who have many CNS symptoms that are attributable to primary neurologic damage (e.g., chemical intoxication, encephalitis, strokes) from those whose complaints of CNS dysfunction are attributable to other causes (e.g., stress, depression, somatization disorders, malingering). VA has recently funded a multi-center cooperative study that will develop a brief computer-assisted neuropsychological screening battery that will differentiate patients with primary neurologic diseases from those without neurologic disorders. A secondary aim of the study is to develop brief batteries with high sensitivity to specific neurologic disorders.

Treatment of PTSD

There are many treatment approaches to PTSD, but few, if any, have undergone rigorous testing for efficacy. VA recently funded a new multi-site treatment trial investigating the efficacy of trauma-based group therapy in the treatment of PTSD.

In addition, VA has issued a Program Announcement requesting proposals for additional multi-site trials of PTSD treatment. Researchers who submit proposals are requested to focus on treatment of special subpopulations (women, Gulf War veterans, etc); studies of PTSD and comorbid disorders requiring special treatment; and studies of treatment effects on "preclinical" markers.

Follow-up of Case-Control Study in 24th Seabees (DoD-65)

DoD is providing funds to Dr. Robert Haley from the University of Texas Southwest Medical Center to conduct follow-up studies based on his research published in early 1997 in the Journal of the American Medical Association (Haley et al., 1997a b, and Haley and Kurt 1997). In his original research Haley et al., 1997b detected mild peripheral nerve function deficits in 23 highly symptomatic members of the 24th Seabees. None of these subjects, however, had any clinical manifestations of peripheral neuropathy. As with previously published studies of others, Haley and Kurt (1997) show a relationship between self-reported neurological symptoms and self-reported exposures to potential neurotoxic agents. Because of the select nature of his study population and methodological problems with the analysis, including no established causal association or control for previous exposures, one cannot generalize these findings to the Gulf War veteran population.

The primary goal of DoD's funded effort is to attempt validation of Dr. Haley's initial epidemiological observations of six syndromes and to develop a hypothesis that can be tested. Dr. Haley's general approach is selection of a small number of veterans who meet criteria for his typical neurological syndromes and match them with control groups of well veterans, both deployed and non-deployed. Dr Haley will apply numerous neurological and neurophysiological tests to identify which test can best distinguish a case from controls. The research initiatives focus on understanding the medical consequences of possible sub-clinical exposure to chemical agents and chemical interactions, and on the development of more sophisticated diagnostic tests that may elucidate some of the many individual components that may constitute Haley's six syndromes

Mycoplasma Research (DoD-66)

Researchers at the Walter Reed Army Medical Center, the Armed Forces Institute of Pathology, and the University of California, Irvine, are collaborating with Dr. Garth Nicolson of the Institute of Molecular Medicine in Irvine, CA.

The group has developed a scientifically sound research plan to definitively explore the putative link between *Mycoplasma fermentans*

and Gulf War veterans' health. The initial phase of this research plan is to teach others the laboratory methods associated with the tests Dr. Nicolson has developed (called Nucleoprotein Gene Tracking and Forensic Polymerase Chain Reaction, PCR). These tests will be evaluated to ensure their validity/utility. Based on the results of this initial work the study will expand to investigate the putative links among service in the Gulf, mycoplasma infection, and symptoms.

Two New VA Investigator-Initiated Research Projects

Two new research projects have been awarded funding through the VA Office of Research and Development/Medical Research Service's investigator-initiated Merit Review Program. These two projects were among hundreds of investigator-initiated proposals submitted for central peer review by subcommittees of Medical Research Service's Merit Review Committee, a federally chartered committee of scientific experts. They were awarded funds after rigorous peer-review and secondary review for relevance to VA's mission.

Cross-Sensitization as a CNS Model for Gulf War Chemical Sensitivities (VA-48)

The underlying hypothesis of this research to be conducted at the Tucson VAMC is that Gulf War veterans have acquired chemical intolerance (ACI). This hypothesis is based on a model of neural sensitization, which is the progressive amplification of a given response over the course of repeated, intermittent exposures to a particular stimulus. The researchers further hypothesize that cross-sensitization between multiple pre-War, War, and post-War factors could account for the clinical patterns in certain Gulf War veterans.

Four groups of subjects matched by age, sex, and education, will be used in this research: (1) healthy Gulf War veterans; (2) ill veterans with increased chemical intolerance attributed to military service; (3) ill veterans without increased chemical intolerance; (4) healthy Gulf War era veterans. Subjects will be exposed to jet fuel and sham exposures. Blood pressure, heart rate, eyeblink reactions, startle response, reaction times, and vigilance task performance will be used as outcome measures.

Sensitivity to Pyridostigmine Bromide: Persistent Neural Dysfunction (VA-49)

The hypothesis of this research at the East Orange VAMC addresses two assumptions that were the basis for the use of PB during the Persian Gulf war as a prophylactic against nerve gas exposure. The first assumption is that prophylactic levels of pyridostigmine bromide did not alter central nervous system activity. The second assumption is that its peripheral side effects were transient.

The first study will determine the pharmacokinetics of PB in two strains of rats. The second study will compare the effects of two cholinesterase inhibitors, edrophonium (EDRO) and neostigmine (NEO) to PB on measure of erythrocyte(E-) cholinesterase activity, BuChE activity, and on startle response. The third study will examine whether persistent startle sensitization after exposure to prophylactic levels of PB in rats with abnormal BuChE activity is mediated by central, as opposed to peripheral, nervous system dysfunction. The fourth study will determine how long enhanced startle responsivity lasts after appearance and the nature of the enhanced responsivity in rats with abnormal BuChE activity. Study five will attempt to produce delayed-onset startle sensitization in rats with otherwise normal session of tailshock stress. The last study will directly evaluate the scavenger hypothesis as a possible mechanism for the persistent startle sensitization in one strain of rats.

Development of a Strategic Plan for Research on the Health Effects of Low-Level Exposure to Chemical Warfare Nerve Agents

The 1996 revision of *A Working Plan for Research on Persian Gulf Veterans' Illnesses* (PGVCB, 1996b) recommended that the Federal Government develop a separate strategy for research on the long-term health effects of low-level exposure to chemical warfare nerve agents. This recommendation arose from the observation that there was a distinct lack of research data on nerve agent health effects at subclinical exposure levels.

A subcommittee of the Research Working Group was formed to develop this strategic plan. It has undergone review by the full Research Working Group.

For the purpose of the strategy "low-level" exposure has been defined as:

> *an exposure that results in minimal reduction in acetylcholinesterase with no or minimal observable clinical signs and, in the case of humans, subjective symptoms. For the purposes of dose-response studies, the following gradation of* ***low-level*** *exposures is made:*
>
> - *Level 1:* An exposure that results in no clinical signs (and for humans no subjective symptoms), and minimal AChE inhibition (0-20% reduction in red blood cell AChE).
>
> - *Level 2:* An exposure that results in no clinical signs (and for humans no subjective symptoms), and moderate AChE inhibition (>20% reduction in rbc AChE).
>
> - *Level 3:* An exposure that results in mild clinical signs including: salivation, miosis, and tachycardia. In humans such an exposure would also lead to mild symptoms such as shortness of breath.

Because tolerance to the immediate clinical effects of organophosphorous nerve agent exposure can occur with repeated exposures or exposures of at least 24 hour duration, it is assumed that the above low-level exposure definitions refer to the effects observed in single exposures of less than 24 hour duration.

Exposure durations and patterns of interest include:

- Single dose exposures

- Repeated dose exposures:
  At least one (1) day between doses
  Cumulative period of dosing no greater than four (4) weeks;.
  A minimum of 8 doses and a maximum of 14.

- Nerve agent exposure combined with other neurotoxic agents (such as insecticides), stress, and other exposures that could interact with nerve agents

The subcommittee established the following goals for research on the health effects of exposure to low-level chemical warfare nerve agents:

- Increase knowledge and understanding of the long-term effects of low-level exposures to organophosphorous chemical warfare nerve agents;

- Understand the toxicology of interactions of nerve agents with other environmental factors such as pesticides, pyridostigmine bromide, heat, and psychological stress;

- Apply new knowledge to assess possibility of a causal link between low-level exposure to nerve agent and long-term effects;

- Use new knowledge to anticipate potential future health problems of exposed veterans;

The strategic plan is presented in its entirety, including objectives and strategies, in Appendix D.

Although elements of the strategic plan have already been implemented as a part of the 1997 DoD BAA, such as new research on the basic mechanisms of sarin toxicity, the next step in this process is the development of a full implementation plan.

B. Development and Approval of Protocol for Phase III of the VA National Survey of Persian Gulf Veterans and their Family Members

The purpose of the VA National Survey of Persian Gulf Veterans (VA-2) is to estimate and compare prevalence of various symptoms, medical conditions, and unexplained illnesses in Gulf War veterans and their family members, and those of non-Gulf War veterans and their family members. The National Survey is a population based study being conducted in three phases.

In Phase I, a questionnaire was mailed to each of 30,000 veterans (15,000 Gulf War Veterans; 15,000 non-Gulf War Veterans). Multiple follow-up mailings were made to increase the response rate. In Phase II, a sample of 8,000 non-respondents was randomly selected and a telephone interview was conducted using a

CATI questionnaire, which includes a question on reasons for refusal. Telephone interviews with the non-respondents assist in assessing potential non-respondent bias and will supplement the postal survey data. In addition, during Phase II, selected self-reported data collected by the postal questionnaire are being validated through records review for 2,000 veterans from each group. Data collection for Phase I is complete and is nearly complete for Phase II.

Phase III is the most challenging part of the National Survey because it involves conducting medical evaluations of approximately 1,000 deployed and 1,000 non-deployed veterans, formed as a subset of participants in Phases I and II, and their immediate family members leading to medical evaluations of approximately 5,000 men, women, and children. Because the National Survey itself is population-based, these veterans and family members must be drawn from across the nation thus creating potential logistical problems.

To design and operationalize Phase III, the VA Office of Research and Development (ORD) brought in the expertise of its Cooperative Studies Program. This program has a long history of designing and conducting complex multi-center drug and treatment efficacy trials. A Planning Committee for Phase III is being headed by the Director of VA's Cooperative Studies Coordinating Center at the Hines VA Medical Center in Chicago, Illinois. The other members of the Planning Committee come from VA National Headquarters and from VA Medical Centers around the country. These are researchers actively engaged in cooperative studies and epidemiology. The Planning Committee developed a comprehensive and detailed protocol to a subcommittee of the Cooperative Studies Evaluation Committee (CSEC, a federally chartered advisory committee) for an expedited mail review. The subcommittee approved the protocol for implementation.

Phase III will be carried out at approximately 18 VA Medical Centers (to be named) across the country, allowing veteran participants to drive to these locations. VA Medical Centers that participate will have major university affiliations. The veterans will be examined at the VA Medical Centers, while the spouses and children will have examinations performed under contract to affiliated university medical centers. The medical evaluations are designed to test the following a priori hypotheses:

Primary hypotheses:

Gulf War veterans will have an increased prevalence of the following medical and psychological conditions frequently reported in the literature compared to a control group of non-deployed era veterans:

- Chronic Fatigue Syndrome
- Fibromyalgia
- Post-traumatic stress disorder (PTSD)
- Neurologic abnormalities, including peripheral neuropathy and cognitive dysfunction, and
- Measures of general health status

Secondary hypotheses:

The medical conditions that have been reported as more frequent among Gulf War veterans compared to nondeployed veterans will be of greater prevalence among deployed Gulf War veterans upon objective clinical examination. These include arthritis, dermatitis, hypertension, bronchitis, and asthma.

The prevalence of the above medical conditions in the primary hypotheses and secondary hypotheses will be greater among the spouses of Gulf War veterans than among spouses of nondeployed veterans.

The prevalence of medical conditions and major birth defects found on a pediatric physical examination in the children conceived after the war will be greater for Gulf War veterans than for nondeployed veterans.

Subject enrollment into Phase III is expected to take approximately 18 months.

C. Strategies for Future Deployment Health

1. National Science and Technology Council (NSTC)

As the PAC investigated the wide range of government health-related activities leading up to, during, and following the Gulf War, it identified a number of deficiencies in these activities that have contributed to current problems and controversies relating to Gulf War veterans' illnesses. A major outcome of a recommendation contained in the Final Report of the Presidential Advisory Committee on Gulf War Veterans' Illnesses has been the issuance of a Presidential Review Directive (PRD) instructing the National Science and Technology Council (NSTC) to develop an interagency plan to address future deployment health. Implementing this recommendation is significant in that it recognizes the importance of planning for the future while learning from the past.

PRD/NSTC-5 was issued in April, 1997. Since that time a Task Force composed of four working groups (deployment health, research, records, and risk communication) have each been developing strategic plans for their respective areas. These separate strategic plans were submitted to the Office of Science and Technology Policy of the Executive Office of the President in January 1998 for merging into one single strategic plan. A consolidated draft plan will be submitted to the President's Council of Advisors on Science and Technology (PCAST) for review and comment. A revised plan will then be submitted to NSTC in early spring, 1998, for final review and concurrence. Publication of the final plan, approved by the departments, is anticipated shortly thereafter.

This strategic plan will provide a broad road map for all relevant departments to follow to ensure that the health of deployed servicemembers is optimal. Furthermore, it will enable the government to readily ascertain the nature and extent to which deployments affect the health of servicemembers.

2. National Academy of Science/Institute of Medicine

DoD also requested the advice of the NAS and IOM on a long-term strategy for protecting the health of our nation's military personnel when deployed to unfamiliar environments. The project will draw on the lessons of the Persian Gulf War and subsequent deployments as well as a variety of other evidence to offer recommendations for: (1) an analytical framework for assessing the risks to deployed forces from a variety of medical, environmental, and battle-related hazards, including chemical and biological agents (CBA); (2) improved technology and methods for detection and tracking of exposures to these risks; (3) improved technology and methods for physical protection and decontamination, particularly of CBA; and (4) improved medical protection, health consequences management and treatment, and medical record keeping. The study began in October 1997 and will be completed by October 2000.

This strategic plan will serve as an important complement to the NSTC-5 strategic plan. Whereas the NSTC-5 plan will provide a broad road map for the government to follow, the NAS/IOM plan will provide a greater level of detail.

D. Plume Model of Exposure Associated with the Release of Sarin at Khamisiyah, Iraq

During 1997, the DoD Office of the Special Assistant for Gulf War Illnesses and several Defense agencies collaborated with the Central Intelligence Agency (CIA) to model the potential hazard associated with the accidental release of nerve agent during demolition operations in Iraq after the Gulf War (CIA, 1997). The resulting analysis provides the government's best estimate of the potential exposure of U.S. troops resulting from demolition of munitions at the Khamisiyah Depot in southern Iraq on March 10, 1991.

To develop exposure model predictions DoD solicited the assistance of the Institute for Defense Analysis (IDA, 1997), which convened an expert group that examined the problem and advised on the technical approach. The joint DoD/CIA team undertook initiatives to reduce the uncertainties of the model. To this end, rocket experiments at Dugway Proving Grounds and soil and wood evaporation tests led to greatly refined characterizations of the amount and mechanism of agent release. In addition, the team extensively analyzed weather conditions, including the local scale air circulation, which is central to producing accurate model predictions.

The model analysis used an ensemble approach in which different models were used to reconstruct the meteorology and disperse the agent. The trajectory analysis started with a global-scale analysis of ambient meteorology. This was further refined by mesoscale modeling of the effects of local scale conditions (e.g. enhance moisture flux due to the adjacent marsh and the Persian Gulf sea breeze effect) and local dynamic thermal stability on the plume simulation.

A panel of expert government and non-government atmospheric scientists (Dr. Richard Anthes of the University Corporation for Atmospheric Research (UCAR), Dr. Steven Hanna of George Mason University, Dr. Bruce Hicks of the National Oceanographic and Atmospheric Administration (NOAA) Air Resources Laboratory, and Dr. Will Pendergrass of NOAA's Oak Ridge Atmospheric Turbulence and Diffusion Division) conducted an independent review of the modeling. The panel concluded that the resulting estimates "produced credible predicted concentrations for use in determining the area where service personnel might have been exposed to significant health impacts due to hazardous chemicals...". The panel further opined that "Conservative assumptions about the source term (i.e., probably erring on a high side estimate) further support this important conclusion that the probability that service personnel were exposed to hazardous concentrations is quite small."

The modeled hazard and resulting dosage "footprint" provide the best estimate of the nerve agent hazard and will be important for epidemiological research. DoD will develop exposure profiles for individual troop units that estimate the hazard exposure over time. That information will be made available to epidemiological researchers.

E. Review of Status of Serological Testing for Leishmaniasis

In June 1997 researchers at the Portland VA Environmental Hazards Research Center (PEHRC) reported preliminary results from experimental *L. tropica* serological testing conducted by the University of Washington, Infectious Disease Research Institute and Corixa Corporation on 102 serum samples (this number later increased to 200). These samples were from Gulf War veterans participating in a case-control study at PEHRC. Approximately two thirds of the samples provided were identified by the PEHRC as cases. The working case definition developed by the PEHRC is defined as follows:

A "Case" is a respondent who must have at least one of the following signs or symptoms:

- *Muscle/joint pain*
- *Cognitive changes including memory loss, confusion, inability to concentrate, mood swings, and/or somnolence*
- *Diarrhea*
- *Skin or mucous membrane lesions*
- *Unexplained fatigue*

Onset must have been during or after deployment to the Gulf War. Symptoms must have persisted for one month or longer and occurred during the three-month period preceding a clinical evaluation.

Healthy controls and cases were identified from responses to a mailed questionnaire. Cases and controls received a medical workup at the Portland VAMC. To be selected as a case, a veteran's symptoms could not be explained by a diagnosable medical condition.

Dr. Steve Reed of the Infectious Disease Research Institute and Corixa Corporation performed the serological tests using an experimental procedure. Of the 102 samples provided by the PEHRC, 10 had elevated antibody titers to a synthetic *L. tropica* antigen. Of these 10, 6 (or 60%) were cases, 2 were controls, and 2 were neither (the latter individuals were originally cases whose symptoms resolved at the time of physical examination). The ratio of positive PEHRC-defined cases to the total number of samples that tested positive (60%) was approximately equal to the overall proportion of cases in the total set of 102 serum samples tested, suggesting that the number of cases who tested as seropositive reflected the proportion of cases in the 102 samples.

The observation that 6 of the 10 samples testing positive were cases, however, raised concerns that *L. tropica* might be more prevalent than originally thought among Gulf War veterans (only 32 clinically-proven cases of leishmaniasis (viscertropic and cutaneous) had been identified in Gulf War veterans prior to these findings).

There was also concern over the safety of the US blood supply if indeed *L. tropica* infection was prevalent among Gulf War veterans. Lastly, the subcommittee identified a potential ethical problem because the experimental serologic test that was performed on subjects' sera at PEHRC could not provide subjects reliable, clinically significant information in the event of a positive test.

To resolve these questions and concerns several meetings of a subcommittee of the RWG were held in Washington, DC and in Portland, OR between July and September 1997. Besides members of the RWG, experts on *L. tropica,* and blood supply safety and monitoring from inside and outside the government were consulted. The overall purpose of the meetings was to:

- Evaluate the validity of Corixa Corporation's experimental serological assay;
- Evaluate the interpretability of the preliminary PEHRC data;
- Establish an understanding of the implications, if any, to veterans and the general public;
- Establish a set of action items.

A full report on these meetings is in Appendix E.

As part of its evaluations the subcommittee met with researchers from the PEHRC, the University of Washington Infectious Disease Research Institute, and Corixa Corporation in Portland, OR. At the meeting the subcommittee learned that at that time there was no apparent relationship between the results of the serologic *L. tropica* test and Gulf War veterans' current symptoms or medical status. This information was derived from two sets of presentations provided to the subcommittee. One set was about the PEHRC case control study being conducted at the PEHRC. The other was a presentation by Dr. William Reeves of the CDC on his investigations of the 193rd Pennsylvania Air National Guard. Serum samples from these veterans were given to Corixa for serologic testing using the same methodology as was used for the PEHRC study.

At the end of its evaluations the subcommittee concluded:

1. The experimental serologic test for *L. tropica* infection should be viewed as preliminary and as a research hypothesis-generating tool. The evidence from the Portland EHRC study, though suggestive, could not be used to conclude that there was *L. tropica* infection among Gulf War veterans. A determination of infection prevalence would have to wait for improved antibody testing.

2. Based on historical records, there is no evidence, beyond five documented cases in England, of blood-blood transmission of leishmaniasis in the worldwide population. Therefore, evidence presented did not support a ban on donations of blood from Gulf War veterans.

The subcommittee identified specific future directions to improve the potential for development of a reliable serologic assay for *L. tropica* infection. It recommended the development of a "qualification panel" of reference positive and negative sera that could be used to identify promising, candidate serologic assays for small-scale studies such as the PEHRC study. It was then recommended that long-term development of a "validation" panel with a large number of pedigreed positive and negative sera that could be used for accurate determinations of assay sensitivity and specificity be undertaken.

Subsequent information on the ability to obtain sufficient documented true positive and true negative sera samples makes the above recommendations difficult to fulfill. However, advances in the development of an antigen skin test (DoD-8B) are promising and will be emphasized.

F. HHS Report to Congress on Multiple Chemical Exposures and Gulf War Veterans Illnesses

In response to House Report 105-205, in December 1997 HHS submitted to Congress a report (HHS, 1998) on its plans to carry out a research program on the health effects of exposure to multiple chemicals. The report provides the Department's initial plans for the 1998 fiscal year.

The principal goal for FY'98 is to develop a five-year research plan to investigate the potential relationships between biological and chemical exposures in the Gulf War and

subsequent illnesses in Gulf War veterans. One of the first activities will be a conference. The conference will strive to fully characterize the nature of multiple exposures within the Gulf War veteran population and to relate this characterization to what is known about multiple chemical sensitivity (MCS) and related conditions and disorders within the civilian population. It is expected that the conference will develop a research plan that builds upon existing efforts to understand MCS and related conditions within the context of the known environmental exposures during the Gulf War. It is expected that the plan will focus on individual factors that could affect susceptibility to low-level chemical exposures, and on the development of acceptable case criteria for MCS that can be used in future clinical and epidemiological research.

In addition to this, in FY'98 HHS will augment funding for an existing NIH Grant Announcement entitled "Chemical Mixtures in Environmental Health" (RFA: ES-98-002, NIH Guide, Volume 26, Number 38, November 21, 1997). This announcement is a joint effort of the National Institute of Environmental Health Sciences (NIEHS) and the Environmental Protection Agency (EPA). The announcement seeks to fund research projects that will expand knowledge involving the characterization of "real-life" chemical mixture exposures based on human exposure or human body burden and to better understand the mechanisms of action involved as they relate to human health. Funding announcements are anticipated for summer 1998.

G. NAS/IOM Assessment of the Health Effects Associated with Service in the Gulf War

The ultimate value of the government's investment in research on Gulf War veterans' illnesses can only be realized when general conclusions can be drawn regarding such issues as the nature and cause(s) of the illnesses affecting Gulf War veterans. An assessment must encompass all research, whether directly related to the illnesses of Gulf War veterans, or indirectly related but highly relevant. Because of the important policy implications surrounding such an assessment, VA followed the advice of the PAC in its Special Report (PAC, 1997) to contract for the assessment with an independent scientific organization. VA chose to contract with NAS/IOM to carry out the assessment.

The project will be conducted in three phases. During this first phase, criteria will be developed for the identification of health outcomes of interest and for the selection of exposures to be examined. A review of the literature regarding some prototypic exposure-health effect associations will be conducted to develop methods to be used for analysis and synthesis of different types of research findings, e.g., animal toxicology data, occupational exposure data, and epidemiological data. In conducting reviews the committee will, for each medical condition considered, assess the latency periods, if any, between exposures to the potential risk factors and the manifestation of illnesses.

Scientific evidence concerning association of exposures and illness will be examined taking into account the strength of the scientific evidence and the appropriateness of the methods used to identify associations; whether the evidence indicates the levels of exposure of the studied populations were comparable to the exposures of Gulf War veterans, and whether there exists a plausible biological mechanism or other evidence of a causal relationship between exposure to the risk factor or factors and the medical conditions.

During phase two the remaining exposures will be subject to review and analysis. The final phase will be a series of updates of the literature and the associations, to be conducted every two or three years. An important aspect of this assessment is the development of research recommendations to fill identified gaps in knowledge.

H. Measuring the Health of Gulf War Veterans.

Longitudinal follow-up of the health status of Gulf War veterans is challenging, especially for ill-defined or undiagnosed conditions. VA and DoD have contracted with NAS/IOM to develop a research design(s) and methods that could be used to measure the health of Gulf War veterans. The committee will (1) discuss potential research questions regarding Gulf War veterans' health status, health outcomes, and treatment efficacy, (2) examine the strengths and limitations of existing data bases for the conduct of research on health status, health outcomes, and treatment efficacy, (3) make recommendations to supplement of these data,

and (4) identify specific questions for which the committee will develop approaches and methods for study.

I. New DoD Extramural Research Initiative

In collaboration with the RWG, DoD developed a new research initiative for FY'98 (see Appendix C5 for the full solicitation). Under this initiative DoD solicited new research proposals for studies on the possible health risks associated with service in the Gulf War. The goals of this research are (1) to continue investigation of the pathogenesis of unexplained illnesses of Gulf War veterans; (2) to use the understanding of basic disease mechanisms to help ill veterans, and avoid or reduce the occurrence of such unexplained illnesses in future military deployments. This particular initiative is directed only at U.S. institutions of higher education (other than Federal Government) with degree-granting programs in science and/or engineering, or by consortia led by such institutions. DoD is committed to spend up to $8 million in FY'98 for this initiative. The submission deadline was February 4, 1998.

The specific request is focusing on areas of research interest:

(1) Investigation of the confluence of cognitive, emotional and physical factors which produce chronic, non-specific symptoms and physiological outcomes typical of the undiagnosed illnesses of some Gulf War veterans. Examples of studies sought range from sociological studies of the stress manifestations of military deployment to basic studies of psychoneuroimmunological mechanisms which could elucidate physical symptoms such as muscle weakness, fatigue, and joint pain;

(2) Studies of toxicity and toxic interactions of environmental chemicals, prophylactic drugs, and military materiel. Examples of studies sought in this topic include, but are not limited to, improved understanding of health effects of combinations of exposures specific to the Gulf War (including jet fuel vapor, pesticides and insect repellents, and pyridostigmine bromide), studies of biomarkers to denote individual exposure to toxic substances, and the development of near-real time bioassays and bioelectronic sensor technologies for assessment of toxicological hazards in future deployments. This latter research should emphasize identification of fundamental physiological endpoints in bioassays which could be applied to bioelectronic sensor development to identify hazards from unidentified chemicals and chemical mixtures;

(3) Studies of long-term health consequences associated with exposure to subclinical levels of chemical warfare agents. Examples include epidemiological studies of soldiers who may have been exposed to chemical warfare agent without acute symptoms and epidemiological studies on the health consequences of exposure in populations, such as passengers present during the Tokyo subway attack and individuals who participated in chemical agent research or worked in production plants or storage facilities.

V. RESEARCH MANAGEMENT

A. Overview

Research on Gulf War veterans' illnesses is a complex undertaking, involving a number of different approaches. The federal research effort on this problem involves scientists in federal, academic, and private institutions, both in the United States and abroad, conducting research sponsored by VA, DoD, and HHS. Each of these Departments has distinct, though complementary, capabilities and capacities for conducting and sponsoring research on Gulf War veterans' health issues. In addition, each Department has its own appropriation for extramural and intramural general biomedical research programs.

The biomedical research programs in VA, DoD, and HHS have well established management structures for science policy formulation and the solicitation, scientific peer review and funding of both extramural and intramural programs. Each department's research management hierarchy for Gulf War veterans' illnesses research has been linked through an overall policy and management coordination effort carried out by the Research Working Group (RWG) of the Persian Gulf Veteran's Coordinating Board (PGVCB). As an operational policy, RWG works through the line management authority each department maintains over its intramural scientists, scientific program managers (responsible for extramural research), and their budgets. The RWG has no budget authority itself, however. As a consequence, all funds for research flow through the funding agency or department.

B. Oversight of Research

Each Department engaged in research on Gulf War veterans' illnesses endorses the need for both prospective and retrospective scientific peer review of research. Because of the urgency of the health concerns of Gulf War veterans and their families, and the diverse nature of the reported illnesses, review and oversight of research have been important. VA, DoD, HHS, and the Executive Office of the President have established multiple oversight mechanisms to capture the full spectrum of the overall effort; some oversight mechanisms are broad-based, encompassing all research issues, whereas others are more focused on individual research projects and programs.

Three of the most important oversight activities are briefly discussed below. Although each has had a broad mandate encompassing virtually all issues related to Gulf War veterans' illnesses, the discussion below will focus on their research oversight activities, findings, and recommendations.

1. Institute of Medicine/Medical Follow-up Agency (under contract to VA and DoD): Health Consequences of Persian Gulf Service

As directed by P.L. 102-585 section 706, in 1993 VA and DoD jointly entered into an initial 3 year contract with the Medical Follow-Up Agency (MFUA) of the Institute of Medicine (IOM), National Academy of Sciences (NAS). The IOM was charged with reviewing existing scientific, medical and other information on the health consequences of military service in the Persian Gulf area during the Gulf War. The IOM was also mandated to review the research activities and plans of the various involved agencies and make recommendations.

On January 4, 1995, the IOM issued a report entitled "Health Consequences of Service During the Persian Gulf War: Initial Findings and Recommendations for Action" (IOM, 1995). In general the IOM panel endorsed previous findings of the Defense Science Board (DSB, 1994) and a National Institutes of Health Technology Assessment Conference (NIH, 1994) that no single disease entity with no single etiology could be identified for the health complaints expressed by Gulf War veterans. The panel also strongly emphasized the importance of population-based studies, which are currently ongoing in a number of areas. At that time the panel found no evidence that either chemical or biological warfare (CBW) agents were used against coalition troops during the Gulf War and, as a consequence, recommended that this not be a factor in future considerations of the causes of Gulf War veterans' illnesses.

In the final IOM report of September 1996 (which stands as a separate document from its initial January 1995 report) the IOM panel stated that it could find no scientific evidence to date demonstrating adverse health consequences

associated with service in the Gulf War beyond the few documented cases of leishmaniasis, combat-related or injury-related mortality or morbidity, and increased risk of psychiatric sequelae of deployment. The panel went on to state that there is a strong likelihood that no single hypothesis could account for all illnesses reported by Gulf War veterans, whether or not they resulted from service in the Gulf War. Finally, the panel observed that after previous wars and conflicts, a proportion of military service personnel and veterans have had medical complaints of varying degrees of severity that are not explainable based on identifiable health hazards or physical illnesses. This observation echoes work by Hyams et al. (1996) tracing such a phenomenon back at least to the Civil War.

The IOM panel made the following research recommendations:

- Determine factors for possible response differences among active and non-active duty service members;
- Conduct mortality studies on Gulf War veterans out to at least 30 years;
- Determine the reason for excess deaths by external causes among Gulf War and other veterans;
- Continue and extend the Defense Medical Epidemiological Database;
- Refine geographical information systems (GIS) for troop locations and plan for future conflicts;
- Conduct reviews of the Total Exposure Assessment Methodology used to predict pollutant exposure in the Gulf War;
- Study gender issues when assessing health effects of deployment;
- Conduct studies on the consequences of assigning men and women to serve together;
- Complete and publish the Naval Health Research Center epidemiology studies;
- Complete and publish the VA National Survey of Persian Gulf Veterans;
- Complete evaluation of predictors of VA registry enrollment;
- Strengthen the epidemiologic capabilities of the armed forces; and
- Submit all research (intra- and extramural) for peer review publication in a timely manner.

As authorized by P.L. 102-585 sec. 706, the agreement with IOM has been extended for the general purposes of providing core epidemiological support for research on military and veteran populations. This support is a valuable infrastructural base to carry out epidemiological research on Gulf War veterans' illnesses.

2. Department of Veterans Affairs: Persian Gulf Expert Scientific Committee

In late 1993 VA chartered a standing federal advisory committee at the request of VA Secretary Jesse Brown. The purpose of the Expert Scientific Committee is to advise the VA Under Secretary for Health and the Chief Public Health and Environmental Hazards Officer on medical findings affecting Gulf War veterans. The Committee also reviews research activities. The Committee consists of 13 members selected on the basis of high professional achievement, expertise in illnesses that might be related to Gulf War service, research expertise in these areas, and representation of veterans' interests. The Committee has met 12 times since early 1994 and has heard presentations from numerous scientists and clinicians.

The deliberations of the Committee have provided a continuous review of VA clinical and research programs. The Committee has made many recommendations to enhance programs for Gulf War veterans. A subcommittee of the Committee has provided oversight of the VA National Survey of Persian Gulf Veterans.

3. Executive Office of the President: Presidential Advisory Committee on Gulf War Veterans' Illnesses (PAC)

The President established the PAC by Executive Order on May 26, 1995. Between August 1995 and January 1997 the committee met a total of 23 times either as a full committee or in subcommittees. The 12 member committee was composed of scientists, health care professionals, veterans, and policy experts. The Committee was charged with reviewing and providing recommendations on the full range of activities relating to the government's response to Gulf War veterans' illnesses. In addition the Committee evaluated the available data on the nature of Gulf War veterans' illnesses and on potential health effects related to Gulf War risk factors.

The Committee released an interim report in February 1996 (PAC, 1996a). Although the Interim Report stated that VA, DoD, and HHS research programs are generally well-designed and should lead to meaningful answers to issues concerning Gulf War veterans-related health issues, it also had several recommendations. The Committee's recommendations covered issues such as peer review, coordination of agency research activities, the use of public advisory committees and the availability of information on troop exposures. The Committee made no findings about specific illnesses or risk factors in the Interim Report. In response to the Interim Report, the agencies developed a coordinated plan of action (PGVCB, 1996a) that responded to the Advisory Committee's interim recommendations.

The Final Report of the Committee was released in December 1996 (PAC, 1996b). The PAC came to the following conclusions:

- Many veterans have illnesses likely to be connected to service in the Gulf War;
- Current scientific evidence does not support a causal link between the symptoms and illnesses reported today by Gulf War veterans and exposures while in the Gulf to:

  Pesticides

  Chemical warfare agents

  Biological warfare agents

  Vaccines

  Pyridostigmine bromide

  Infectious diseases

  Depleted uranium

  Oil well fires and smoke

  Petroleum products

The Final Report also concluded that stress (known to affect the brain, immune system, cardiovascular system, and various hormonal responses) is likely to be an important contributing factor to Gulf War veterans' illnesses.

The Final Report made the following research recommendations:

- Require any new large-scale epidemiologic studies to have scientific and public advisory committees;
- Develop more accurate and reliable troop locator systems;
- Plan and conduct further research on low-level exposure to organophosphate chemical warfare nerve agents;
- Monitor Gulf War veterans for increased rates of cancer through mortality studies;
- Conduct research on the health status of individuals with embedded depleted uranium fragments;
- Collect and archive serum samples from U.S. service personnel when feasible;
- Conduct basic and clinical research on the physiologic effects of stress and stress-related disorders; and
- The Research Working Group should consult more thoroughly with other federal agencies.

Because of concern over the adequacy of DoD investigations into reports of possible chemical and biological warfare exposure incidents during the Gulf War, and because of a need to follow up on recommendations the Committee's Final Report, the President extended the Committee through October 1997. At that time the PAC issued a Special Report (PAC, 1997). In the Special Report the Committee did not alter its findings and conclusions with respect to potential causes of Gulf War veterans' illnesses. The Special Report did not contain any specific recommendations for research.

With respect to federally funded research on Gulf War veterans' illnesses, the PAC concluded that the government has been adequately and appropriately responding to its recommendations. The PAC particularly commended the government for its new initiatives targeted on health effects of low-level exposure to Chemical Warfare (CW) agents. As the PAC noted in its Final Report, "the amount of data from either human or animal research on low-level exposures [to CW agents] is minimal." However, in its Special Report, the PAC concluded that planned research on the health effects of low-level exposure may address any

uncertainties and inconclusiveness identified in the Final Report.

The PAC approved of the government's targeted solicitations for research and the process used to make such awards. However, the Committee expressed reservations about a perceived degradation in DoD's processes for funding research related to Gulf War veterans' illnesses. The Committee noted that "competition and external peer review of research proposals are essential to guarantee scientific merit, relevance, and level of priority generally." The Committee acknowledged that benefit can accrue from small-scale, short-term funding on a sole source basis for pilot projects or to address narrow scientific questions (e.g., DoD's recent funding of $100,000 for technical issues related to a test for possible *Mycoplasma* infection). The Committee stated, though, that such approaches should be rare and that protocols still should be peer reviewed prior to funding, limited in the amount of funds released, and not subject to renewal without competition.

The RWG of the PGVCB will continue to endorse peer review and competition as the means of obtaining the best research products.

4. Other Oversight

In addition to the broad oversight that has been provided by the three committees cited above, there are several standing and special committees responsible for oversight on individual research projects and programs. Projects and programs receiving continuous or ad hoc oversight include:

- The National Health Survey of Persian Gulf Veterans (VA);
- Health Assessment of Gulf War Veterans from Iowa (HHS); and
- Each of four Environmental Hazards Research Centers (VA).

The RWG also continues to encourage that all large epidemiological studies establish public advisory groups that include representation of Gulf War veterans.

Additionally, congressional oversight committees and the General Accounting Office have provided important input into the research process.

C. Research Coordination

In 1993, VA, DoD, and HHS recognized the importance of a coordinated approach to research on Gulf War veterans' illnesses and formed the "Persian Gulf Interagency Research Coordinating Council". By January 1994, when the Secretaries of VA, DoD, and HHS formed the Persian Gulf Veterans Coordinating Board, the Research Coordinating Council became the Research Working Group operating under the auspices of the Coordinating Board (Beach et al., 1995). Because of the potential link between environmental factors and Gulf War veterans' illnesses, the Environmental Protection Agency was asked to be a member of the Research Working Group. Figure I-1 shows the structure of the Research Working Group. Figure I-1 includes various subcommittees that have been in existence over the past several years. The Planning Subcommittee for Annual Meetings of Federal Researchers has been responsible for organizing two meetings of federally funded researchers, and is currently planning a third. These meetings provide an opportunity for researchers to gather together to share recent research results and to discuss research problems of mutual interest. The Subcommittee for Project Funding Recommendations is established to provide, as appropriate, programmatic reviews of research proposals that have already undergone review for scientific merit (see below for details). The Subcommittee to Develop a Research Strategy for Low-Level Nerve Agent Exposure Health Effects developed a strategic plan in 1997 and is included in Appendix D. The Ad Hoc Subcommittee to Review the Status of Leishmaniasis Research was formed to examine the current status of the development of a serological test for leishmaniasis. The report of the Ad Hoc Subcommittee is in Appendix E.

The RWG is charged with assessing the state and direction of research, identifying gaps in factual knowledge and conceptual understanding, identifying testable hypotheses, identifying potential research approaches, reviewing research concepts as they are developed, collecting and disseminating scientifically peer-reviewed research information, and insuring that appropriate peer review and oversight are applied to research conducted and sponsored by the Federal Government. Membership on the Research Working Group consists of senior research scientists and clinical managers from VA, DoD, HHS, and EPA.

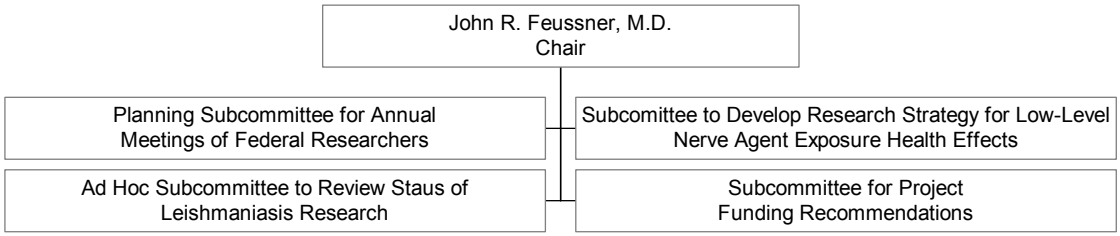

Figure V-1 - Research Working Group Organization

Programmatic Review of Extramural Research Proposals

An important function of the RWG is programmatic review and recommendation to funding agencies of research proposals that have been competitively peer reviewed. Figure I-2 illustrates the general approach the RWG has taken to extramural research (research funded by an agency, but carried out by organizations outside of the agency such as universities, private laboratories, or other independent government agencies). The RWG works collectively with VA, DoD, and HHS to establish research needs and identify agency-specific funding mechanisms to support that research. For a specific research funding activity, the responsible funding agency works with and through the RWG to develop a targeted solicitation for research. Proposals that are submitted to the funding agency in response to a solicitation are scientifically peer-reviewed using agency-specific peer review programs (e.g., DoD/Department of the Army (DA) uses a contract with the American Institute of Biological Sciences). Abstracts of peer-reviewed proposals, written reviews of the peer-reviewers, and the scientific merit scores assigned by the peer-reviewers, are provided to a subcommittee of the RWG charged with providing secondary review of proposals for relevance. This material is redacted for personal and institutional identifiers. Relevance determinations are guided by programmatic needs articulated through the RWG process and reflected in the *Working Plan.* In its secondary review the RWG may re-rank proposals based on relevance, but it will not recommend funding any non-meritorious proposal, irrespective of relevance or funds availability, to any agency.

Though scientists within intramural research programs do not compete for their funding in the same way as non-federal extramural scientists, the RWG works with agencies to ensure that intramural programs and projects are adequately peer-reviewed.

The RWG will continue to work diligently to foster the highest standards of competition and peer-review for all research on Gulf War veterans' illnesses.

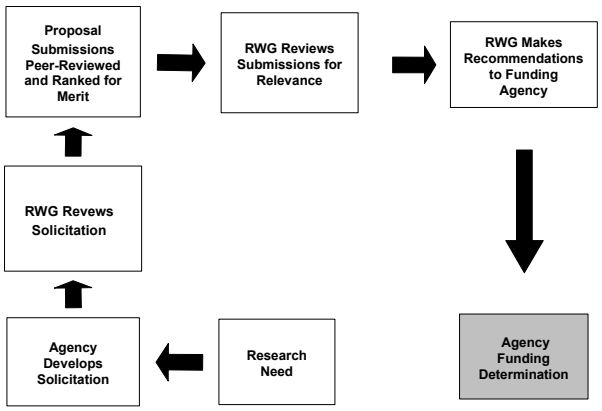

Figure V-2. Research Funding Process

Notable among the activities of the RWG are:

- Development, production, and dissemination of the 1995 *A Working Plan for Research on Persian Gulf Veterans' Illness* (PGVCB, 1995), and its 1996 revision (PGVCB, 1996b);

- Production and dissemination of Annual Reports to Congress for 1994, 1995, and 1996 on progress, status, and results of federal research activities;

- Secondary programmatic review of research proposals submitted to funding agencies;

- Presentations by federal and non-federal researchers before the Research Working Group;

- Organization of meetings of federally funded researchers;

- Organization of an international symposium in conjunction with the Society of Toxicology on the health effects of low-level exposure to chemical warfare nerve agents.

- Development of a strategy for research on the health effects of exposure to low-levels of chemical warfare nerve agents (Appendix D).

- Follow-up investigation of preliminary reports of positive experimental serological tests for leishmaniasis (Appendix E).

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