Department of Veterans Affairs

ANNUAL REPORT TO CONGRESS

Federally Sponsored Research on Gulf War Veterans' Illnesses for 2004

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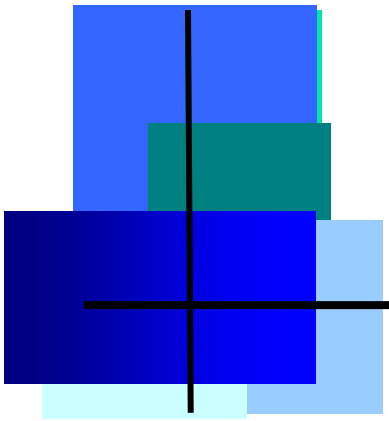
Deployment Health Working Group Research Subcommittee



Annual Report to Congress – 2004

Federally Sponsored Research on Gulf War Veterans' Illnesses for 2004

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Section 707 of Public Law 102-585, as amended by Section 104 of Public Law 105-368, requires that an annual report be submitted to the Senate and House Veterans' Affairs Committees on the results, status, and priorities of research activities related to the health consequences of military service in the Gulf War (Operations Desert Shield and Desert Storm; August 2, 1990 – July 31, 1991). The Research Subcommittee of the interagency Deployment Health Working Group (DHWG) prepared this *2004 Annual Report to Congress*, which is the eleventh report on research and research activities. The DHWG tracks all federally funded research projects related to Gulf War veterans' illnesses.

This Annual Report is divided into five sections. Section I is an introduction. Section II highlights and summarizes research progress published since the last Annual Report. Section III summarizes funding trends for Gulf War research during the period from FY 1996 through FY 2005. Section IV is an analysis of the Federal Government's portfolio of research on Gulf War veterans' illnesses. Section V highlights significant new research projects and initiatives since the last Annual Report.

II. RESEARCH RESULTS IN 2004

Section II provides brief summaries of research on the health problems of Gulf War veterans which was published in English during calendar year 2004. In this annual report, a new categorization scheme for research results is introduced. Research results are grouped according to the 5 Research Focus Areas used to organize the 21 Research Topics (see Section V): Brain and Nervous System Function, Environmental Toxicology, Immune Function and Infectious Diseases, Reproductive Health, and Symptoms and General Health Status. The reduction in the number of primary topics to 5 provides a clearer vision of the scope and depth of the Federal research portfolio on Gulf War veterans' illnesses. In this section, published research results are described followed by specific study abstracts taken from PubMed.

III. RESEARCH FUNDING TRENDS

The Departments of Veterans Affairs (VA), Defense (DoD), and Health and Human Services (HHS) sponsored a total of 267 distinct projects related to health problems affecting Gulf War veterans from fiscal year (FY) 1992 through FY 2004. The scope of the Federal research portfolio is broad, from small pilot studies to large-scale epidemiology studies involving large populations and major center-based research programs. Federal funding for research on Gulf War veterans' illnesses totaled ~$260 million for the period from FY 1995 through FY 2004. As of September 30, 2004, 192 projects were completed (~72% of the 267 projects), and 75 projects (~28%) were new or ongoing.

IV. NEW RESEARCH PROJECTS AND INITIATIVES

VA funded six new projects in FY 2004. The primary research foci of these projects included Brain and Nervous System Function (3), Immune Function and Infectious Diseases (1), and Symptoms and General Health (2). Two of these projects were funded as a result of special solicitations for Gulf War research proposals. Seven additional ongoing projects were added to the VA Gulf War research portfolio as a result of a complete portfolio review in November 2005. The details of this portfolio review will be fully described in the 2005 Annual Report to Congress. HHS funded one new project focused on Brain and Nervous System Function.

V. RESEARCH PRIORITIES

Although the research priorities remain unchanged from previous years, modifications have been made in the organization and analysis of the Federal research portfolio on Gulf War veterans'illnesses. The 21 Research Questions used as the framework for previous Annual Reports have been converted to 21 Research Topics. This change reflects current funding of projects focused on pathophysiological mechanisms and treatment of illnesses affecting Gulf War veterans in addition to epidemiology studies. The second change was to group the 21 topics into 5 major Research Focus Areas. These changes are reflected in Section II (Research Results) and Appendix B (Project Listing by Research Focus Area).

I. INTRODUCTION

The Secretary of Veterans Affairs is required by Section 707 of Public Law 102-585 as amended by Section 104 of Public Law 105-368, to submit an annual report on the results, status, and priorities of research activities related to the health consequences of military service in the Gulf War to the Senate and House Committees on Veterans' Affairs. The Research Subcommittee of the interagency Deployment Health Working Group (DHWG) prepared this 2004 Annual Report to Congress, which is the eleventh report on research and research activities (DHWG, 2004; DHWG, 2005; MVHCB, 2001b; MVHCB, 2002; PGVCB, 1995; PGVCB, 1996b; PGVCB, 1997; PGVCB, 1998; PGVCB, 1999; PGVCB, 2001). The DHWG tracks all federally funded research projects related to Gulf War veterans' illnesses.

This Annual Report is divided into five sections. Section I is an introduction. Section II highlights and summarizes research progress published since the last Annual Report. Section III summarizes funding trends for Gulf War research during the period from FY 1996 through FY 2005. Section IV is an analysis of the Federal Government's portfolio of research on Gulf War veterans' illnesses. Section V highlights significant new research projects and initiatives since the last Annual Report.

II. RESEARCH RESULTS AND STATUS OF THE FIELD IN 2004

In 2004, numerous research studies provided new and detailed information on the health problems of Gulf War veterans. A PubMed search retrieved 80 relevant articles published in English in calendar year 2004. These articles include federally and non-federally funded research, as well as international research. This section provides brief highlights of published research in 2004, followed by PubMed abstracts. Where possible, the source of funding or relevant federally funded project is included with each abstract.

In this report, a new categorization scheme for research results is introduced. This report presents research results based on the 5 Research Focus Areas used to organize the 21 Research Topics (see Section V): Brain and Nervous System Function; Environmental Toxicology; Immune Function and Infectious Diseases; Reproductive Health; and Symptoms and General Health Status. This reduction in the number of primary topics from 9 to 5 provides a clearer vision of the scope and depth of the Federal research portfolio on Gulf War veterans' illnesses.

Brain and Nervous System Function

In 2004, studies of psychological disorders accounted for the majority of brain and nervous system reports. Two studies by Black and co-workers (Black et al., 2004b; Black et al., 2004a) reported higher rates of anxiety disorders in Gulf War-deployed veterans compared to non-deployed military personnel. No regional differences in binding sites in the brain for benzodiazepines (drugs used for anxiety and sedation) were detected between a group of Gulf War veterans with post-traumatic stress disorder (PTSD) and a comparison group of healthy non-deployed veterans (Fujita et al., 2004). Australian Gulf War veterans showed a greater risk of anxiety disorders, affective disorders, and substance use compared to military controls, as well as an elevated prevalence of psychological problems 10 years post-Gulf War (Ikin et al., 2004; McKenzie et al., 2004). Danish Gulf War veterans showed increased psychological stress without detectable neuromotor impairments (Ishoy et al., 2004). Some symptoms of PTSD, such as emotional numbing and hyperarousal, but not others such as re-experiencing and avoidance, were found to increase over time (Thompson et al., 2004). In another study, blood pressure in men with PTSD did not correlate with levels of norepinephrine in cerebrospinal fluid as it did in healthy men (Strawn et al., 2004). The time course for PTSD symptoms varies according to the initial severity of symptoms and several demographic factors (Orcutt et al., 2004). Abnormal anxiety about imagined symptoms and ailments (hypochondriasis) did not account for the increased symptom reporting among Gulf War veterans studied (Noyes et al., 2004).

No differences in distal neuropathies were evident between Gulf War-deployed and non-deployed veterans (Davis et al., 2004); furthermore, those exposed at Khamisiyah (or their spouses) did not have a greater incidence of neuropathies. A different study (Joseph et al., 2004) suggested a lower incidence of peripheral nerve pathology in Gulf War veterans referred for electrodiagnostic testing.

Black, D. W., Carney, C. P., Forman-Hoffman, V. L., Letuchy, E., Peloso, P., Woolson, R. F. et al. (2004a). Depression in veterans of the first Gulf War and comparable military controls. ***Ann.Clin.Psychiatry, 16,*** **53-61. (DoD-058 and HHS-001)**

Depression is a common mental disorder associated with poor health outcomes. The purpose of this study is to examine the prevalence of depression, mental health co-morbidity, illness variables, and quality of life in a sample of military veterans serving during the first Gulf War. The Iowa Gulf War Case Validation Study involved face-to-face evaluations in 1999-2002 of 602 military personnel, either deployed ("deployed veterans") or eligible but not deployed ("non-deployed veterans") to the Gulf. Subjects were sampled by conducting a series of case-control studies nested within a population-based survey of 4,886 military personnel. All subjects were interviewed using the Structured Clinical Interview for DSM-IV (SCID-IV), and a series of semi-structured interviews and validated questionnaires. Best estimate psychiatric diagnoses were assigned based on all available data. One-hundred-ninety-two (32%) of the 602 surveyed veterans met criteria for a current or lifetime depressive disorder (major depression, dysthymia, depressive disorder--not otherwise specified). Depressed non-deployed veterans were more likely to be female and to have served in the Air Force than depressed deployed veterans. There were few significant differences between the depressed deployed veterans and the depressed non-deployed veterans. Depressed deployed veterans had significantly higher lifetime rates of co-morbid cognitive dysfunction (55% vs. 35%), and anxiety disorders (59% vs. 33%)-mainly accounted for by specific phobias (12% vs. 2%) and posttraumatic stress disorder (33% vs. 10%)-than did depressed non-deployed veterans. Lifetime substance use disorders were significantly more frequent in deployed veterans than non-deployed veterans (70% vs. 52%), particularly alcohol disorders (68% vs. 52%). There were no differences in rates of personality characteristics, family psychiatric history, stressors, hypochondriasis, and level of functioning between the two study groups showed no significant differences. Depressive illness is frequent in military samples, as it is in the general population. The prevalence, pattern of co-morbidity, and illness features were similar in deployed veterans and non-deployed veterans, suggesting that the depression suffered by both groups of veterans is qualitatively comparable. The main difference between study groups was that depressed deployed veterans had higher rates than depressed non-deployed veterans of co-morbid anxiety disorders which were hypothesized to be part of the stress-related syndromes seen in those who experience combat.

Black, D. W., Carney, C. P., Peloso, P. M., Woolson, R. F., Schwartz, D. A., Voelker, M. D. et al. (2004b). Gulf War veterans with anxiety: prevalence, co-morbidity, and risk factors. ***Epidemiology, 15,*** **135-142. (DoD-058 and HHS-001)**

BACKGROUND: Veterans of the first Gulf War have higher rates of medical and psychiatric symptoms than non-deployed military personnel. METHODS: To assess the prevalence of and risk factors for current anxiety disorders in Gulf War veterans, we administered a structured telephone interview to a population-based sample of 4886 military personnel from Iowa at enlistment. Participants were randomly drawn from Gulf War regular military, Gulf War National Guard/ Reserve, non-Gulf War regular military, and non-Gulf War National Guard/Reserve. Medical and psychiatric conditions were assessed through standardized interviews and questionnaires in 3695 subjects (76% participation). Risk factors were assessed using multivariate logistic regression models. RESULTS: Veterans of the first Gulf War reported a markedly higher prevalence of current anxiety disorders than non-deployed military personnel (5.9% vs. 2.8%; odds ratio = 2.1; 95% confidence interval = 1.3-3.1), and their anxiety disorders are associated with co-occurring psychiatric disorders. Posttraumatic stress disorder, panic disorder, and generalized anxiety disorder were each present at rates nearly twice expected. In our multivariate model, pre-deployment psychiatric treatment and pre-deployment diagnoses (posttraumatic stress disorder, depression, or anxiety) were independently associated with current anxiety disorder. Participation in Gulf War combat was independently associated with current posttraumatic stress disorder, panic disorder, and generalized anxiety disorder. CONCLUSIONS: Current anxiety disorders are relatively frequent in a military population and are more common among Gulf War veterans than non-deployed military personnel. Pre-deployment psychiatric difficulties are robustly associated with the development of anxiety. Healthcare providers and policymakers need to consider panic disorder and generalized anxiety disorder, in addition to posttraumatic stress disorder, to ensure their proper assessment, treatment, and prevention in veteran populations.

Davis, L. E., Eisen, S. A., Murphy, F. M., Alpern, R., Parks, B. J., Blanchard, M. et al. (2004). Clinical and laboratory assessment of distal peripheral nerves in Gulf War veterans and spouses. *Neurology, 63,* 1070-1077. (VA-002C)
BACKGROUND: The prevalence of symptoms suggesting distal symmetric polyneuropathy (DSP) was reported to be higher among deployed veterans (DV) to the Persian Gulf in 1990-1991 than to control non-deployed veterans (NDV). The authors therefore compared the prevalence of DSP by direct examination of DV and their spouses to control NDV and spouses. METHODS: The authors performed standardized neurologic examinations on 1,061 DV and 1,128 NDV selected from a cohort of veterans who previously participated in a national mail and telephone survey. Presence of DSP was evaluated by history, physical examination, and standardized electrophysiologic assessment of motor and sensory nerves. Similar examinations were performed without electrophysiologic tests in 484 DV spouses and 533 NDV spouses. Statistical analyses were performed with appropriate adjustments for the stratified sampling scheme. RESULTS: No differences between adjusted population prevalence of DSP in DV and NDV were found by electrophysiology (3.7% vs 6.3%, p = 0.07), by neurologic examination (3.1% vs 2.6%, p = 0.60), or by the methods combined (6.3% vs 7.3%, p = 0.47). Excluding veterans with non-military service related diseases that may cause DSP did not alter outcomes. DV potentially exposed to neurotoxins from the Khamisiyah ammunition depot explosion did not significantly differ in DSP prevalence compared to non-exposed DV. The prevalence of DSP in DV spouses did not differ from NDV spouses (2.7% vs 3.2%, p = 0.64). CONCLUSIONS: Neither veterans deployed during the Gulf War era nor their spouses had a higher prevalence of DSP compared to NDV and spouses.

Engel, C. C., Jr. (2004a). Post-war syndromes: illustrating the impact of the social psyche on notions of risk, responsibility, reason, and remedy. *J.Am.Acad.Psychoanal.Dyn.Psychiatry, 32,* 321-334.
The 20th century offered many examples of post-war syndromes such as Da Costa's syndrome, irritable heart, shell shock, effort syndrome, medical evacuation syndrome, post-traumatic stress disorder, and Gulf War syndrome. These post-war syndromes occur under conditions of substantial medical and scientific uncertainty, conditions that potentially magnify the impact of social context on clinical care for these syndromes. This article reviews the social circumstances surrounding four post-war syndromes. The case is made that social context has significantly impacted professional and lay perceptions of causal mediators, relevant risk factors, defining symptoms, and appropriate therapies for these syndromes. Furthermore, it is argued that social context influences what parties are held responsible for post-war syndromes, and what clinical disciplines are ultimately deemed appropriate to provide legitimate post-war illness care.

Fujita, M., Southwick, S. M., Denucci, C. C., Zoghbi, S. S., Dillon, M. S., Baldwin, R. M. et al. (2004). Central type benzodiazepine receptors in Gulf War veterans with posttraumatic stress disorder. *Biol.Psychiatry, 56,* 95-100. (DoD-090)
BACKGROUND: A previous single photon emission computed tomography study showed decreased central type benzodiazepine receptors in the prefrontal cortex in Vietnam War veterans with posttraumatic stress disorder. To assess the generalizability of this finding to patients with more recent history, we studied central type benzodiazepine receptors in Gulf War veterans with posttraumatic stress disorder. METHODS: Nineteen Gulf War veterans with posttraumatic stress disorder and 19 age-matched, healthy, non-deployed veterans participated in a single photon emission computed tomography study using [^{123}I]iomazenil. Regional total distribution volume (V(T)') was compared between two groups using Statistical Parametric Mapping 99 (Wellcome Department of Imaging Neuroscience, London, United Kingdom) and volumes of interest analysis. RESULTS: Benzodiazepine receptor levels did not show regional differences between the two groups, either with or without global normalization. Average difference in V(T)' was 2% across brain areas; however, by applying global normalization, V(T)' in the patient group showed significant negative correlation with childhood trauma scores in the right superior temporal gyrus. CONCLUSIONS: Less severe symptoms and shorter duration of the illness in the current group than the prior one may be the source of the difference in the results of the two studies.

Ikin, J. F., Sim, M. R., Creamer, M. C., Forbes, A. B., McKenzie, D. P., Kelsall, H. L. et al. (2004). War-related psychological stressors and risk of psychological disorders in Australian veterans of the 1991 Gulf War. *Br.J.Psychiatry, 185,* 116-126. (Australian Department of Veterans' Affairs)
BACKGROUND: Questions remain about the long-term health impacts of the 1991 Gulf War on its veterans. AIMS: To measure psychological disorders in Australian Gulf War veterans and a military comparison group and to explore any association with exposure to Gulf War-related psychological stressors. METHOD: Prevalences of DSM-IV psychological disorders were measured using the Composite International Diagnostic Interview. Gulf War-related psychological stressors were measured using a service experience questionnaire. RESULTS: A total of 31% of male Gulf War veterans and 21% of the comparison group met criteria for a DSM-IV disorder first present in the post-Gulf War period. The veterans were at greater risk of developing post-Gulf War anxiety disorders including post-traumatic stress disorder, affective disorders and substance use disorders. The prevalence of such disorders remained elevated a decade after deployment. The findings can be explained partly as a 'war-deployment effect'. There was a strong dose-response relationship between psychological disorders and number of reported Gulf War-related psychological stressors. CONCLUSIONS: Service in the 1991 Gulf War is associated with increased risk of psychological disorders and these are related to stressful experiences.

Ishoy, T., Knop, J., Suadicani, P., Guldager, B., Appleyard, M., & Gyntelberg, F. (2004). Increased psychological distress among Danish gulf war veterans--without evidence for a neurotoxic background. The Danish Gulf War Study. *Dan.Med.Bull., 51,* 108-113. (HHS-005)
INTRODUCTION: Compared with controls, up to six years after their return, Danish Gulf War veterans have a significantly higher prevalence of self-reported neuropsychological symptoms, potentially as a result of neurotoxic exposure during deployment. We tested the hypotheses that: 1) GW veterans would perform less well than controls using a computerized neuromotor test battery; and that 2) GW veterans have a psychological profile different from that of controls. MATERIAL AND METHODS: A cross-sectional study of 686 subjects who had been deployed in the Persian Gulf within the period August 2, 1990 until December 31, 1997; the control group comprised 231 subjects matched according to age, gender and profession. All participants underwent clinical and paraclinical examinations, along with a neuromotor test battery (CATSYS Test System) and a psychological health status questionnaire, the SCL-90-R rating scale. RESULTS: No differences were found between GW veterans and controls with respect to lifestyle and cohabitational characteristics. Differences between the two groups with respect to neuromotor function were very small. Within the GW veteran group, stratified according to clustering of neuropsychological symptoms, and stratified according to SCL-90-R score, no trends were found suggesting reduced motor function with increasing symptoms. Of nine dimensions constructed on the basis of the SCL-90-R items, six were significantly associated with being a Gulf War veteran. Statistically, the strongest associations were found for ratings of the obsessive-compulsive dimension and of the depression dimension. No associations were found with respect to phobic anxiety, paranoid ideation, and psychoticism. INTERPRETATION: The increased psychological distress found among Danish GW veterans seemed rather due to a mentally distressing environment than to neurotoxic exposure.

Joseph, T. K., Foster, L., & Pasquina, P. F. (2004). Decreased prevalence of peripheral nerve pathology by electrodiagnostic testing in Gulf War veterans. *Mil.Med., 169,* 868-871. (DoD)
OBJECTIVE: The objective was to report the results of electrodiagnostic testing performed on 56 U.S. Persian Gulf War (GW) veterans versus 120 U.S. non-Persian Gulf War (N-GW) patients referred to a physical medicine and rehabilitation clinic. DESIGN: A retrospective review of medical records was conducted. MATERIALS AND METHODS: Patient medical records of U.S. GW and N-GW patients were reviewed. Patient demographics, reason for consultation, and results of electrodiagnostic testing were extracted from both groups. Results were recorded as positive (abnormal) or negative (normal) occurrence of radiculopathy, generalized peripheral polyneuropathy, and mononeuropathy. The results were then compared using Fisher's exact test. RESULTS: Of the patients referred to rule out a radiculopathy, one of the GW patients (1 of 73) had a positive study, whereas 9 of 38 N-GW patients had positive studies ($p = 0.000$). There was no statistically significant difference between the two groups with respect to the presence of generalized peripheral polyneuropathy or mononeuropathy. CONCLUSION: This retrospective review of medical records reveals no objective evidence from electrodiagnostic testing of an increased incidence of neuromuscular disease in GW veteran patients compared with N-GW patients. On the contrary, our results reveal a statistically lower incidence of positive electrodiagnostic testing within the GW veteran group, suggesting a lower threshold for referral of GW veteran patients for electrodiagnostic testing than N-GW patients.

Kasarkis, E. J., Dominic, K., & Oddone, E. Z. (2004). The National Registry of Veterans with Amyotrophic Lateral Sclerosis: Department of Veterans Affairs Cooperative Studies Program (CSP) #500a. *Amyotroph.Lateral.Scler.Other Motor Neuron Disord., 5 Suppl 1,* 129-132. (VA-089)
In response to concern about the development of ALS among veterans of the U.S. armed forces, particularly Gulf War veterans, the Department of Veterans Affairs established a national registry of veterans with ALS. This Registry will identify living veterans with ALS, track the progression of their disease, and serve as a vehicle to facilitate study of epidemiological risk factors for ALS in a military context. The Registry will also function as a means of communication with the enrolled patients about basic and clinical ALS-specific research. Executive and scientific research committees guide the activity of the registry.

McKenzie, D. P., Ikin, J. F., McFarlane, A. C., Creamer, M., Forbes, A. B., Kelsall, H. L. et al. (2004). Psychological health of Australian veterans of the 1991 Gulf War: an assessment using the SF-12, GHQ-12 and PCL-S. *Psychol.Med., 34,* 1419-1430. (Australian Department of Veterans' Affairs)
BACKGROUND: Elevated rates of psychological morbidity and symptomatology have been widely reported in 1991 Gulf War veterans. The present study used brief self-report instruments to compare the psychological health of Australian Gulf War veterans with that of a randomly sampled military comparison group. METHOD: The 12-item Short Form Health Survey (SF-12), 12-item General Health Questionnaire (GHQ-12), Posttraumatic Stress Disorder Checklist--Specific (PCL-S) and Military Service Experience (MSE) questionnaire were administered to 1424 male Australian Gulf War veterans and 1548 male Australian Defense Force members who were operational at the time of the Gulf War conflict, but were not deployed there. RESULTS: The Gulf War veterans exhibited poorer psychological health, as measured by the above three instruments, than the comparison group members. For Gulf War veterans, the number of stressful experiences, as measured by the MSE questionnaire, was correlated with scores on the three instruments. SF-12 mental health component summary scores and PCL-S caseness, but not GHQ-12 caseness, differed significantly between Gulf War veterans and comparison group members who had been on at least one active deployment. CONCLUSIONS: More than a decade after the 1991 Gulf War, Australian Gulf War veterans are exhibiting higher levels of current (past month) psychological ill-health, as measured using the GHQ-12 and PCL-S, as well as lower mental health status, as measured by the SF-12, than the comparison group. Although not a replacement for formal psychiatric diagnosis, instruments such as those above may aid in the assessment of veterans' psychological health.

McLean, S. A. & Clauw, D. J. (2004). Predicting chronic symptoms after an acute "stressor"--lessons learned from 3 medical conditions. *Med.Hypotheses, 63,* 653-658.
Stressful events occur in the lives of millions of individuals each year. Such events, or "stressors", are experiences that threaten personal well-being, and include traumatic events such as motor vehicle collision, infectious illness, and situations such as military deployment. While most individuals recover from such events, others develop persistent somatic symptoms, such as chronic pain and fatigue, and/or psychological disturbances, such as posttraumatic stress disorder. Recent findings from the study of risk factors for the development of chronic somatic symptoms after a traumatic, infectious, or situational stressor suggest that similar pre-event, event-related, and post-event risk factors influence the development of chronic symptoms in each condition. Females, and those with pre-event distress or psychological factors, may be at higher risk of developing chronic symptoms after such events. Regarding the event, or "stressor", it appears as though the intensity or specific characteristics of exposure may be a relatively unimportant predictor of patient outcome. Instead, other factors such as the worry, or expectation, of chronicity may increase the risk of chronic symptom development. After the event, inactivity and time off work appear to increase the risk of chronic symptoms. Health care providers have an important role in emphasizing the benefits of resuming usual activities, and downplaying potential benefits of continuing in the sick role (e.g., time off work, increased family attention). While many aspects of the complex interaction of biological, psychological, and social factors that influence patient outcome after a stressful event remain to be elucidated, it appears that for the present, one of the most important interventions is to continue to emphasize to patients the old saying, "rest makes rust."

Menon, P. M., Nasrallah, H. A., Reeves, R. R., & Ali, J. A. (2004). Hippocampal dysfunction in Gulf War Syndrome. A proton MR spectroscopy study. *Brain Res., 1009,* 189-194. (VA)
The pathogenesis of Gulf War Syndrome (GWS) is not clearly understood. Data exist to suggest that GWS may originate from a combination of chronic fatigue and sensitivity to the exposure of exogenous agents. Since the head region of hippocampus is highly vascularized and thus vulnerable to toxic substances in

circulation, we postulated that hippocampal impairment occurs in GWS. To test this, single volume localized in vivo proton MR spectroscopy (MRS) studies of the left and right hippocampi of consenting Gulf War veterans (N=15; 10 with GWS, and 5 without GWS) and control Vietnam veterans (N=6) were conducted in accordance with approved human study protocols. The N-acetyl aspartate (NAA) to creatine and choline to creatine ratios were computed from the spectra. The NAA/creatine ratio of the GWS group (N=10) was found to be significantly lower than that of the entire control group (N=11) or the unaffected GW control group (N=5). No laterality differences were observed among any of the three groups. The choline/creatine ratio of the GWS group was not different from that for either control group. To check the existence of any relationship between age and the NAA/creatine ratios, the entire study population was grouped into those below or above the median age (44.3 years). It was found that the NAA/Cre ratio of the younger group (only Gulf War veterans) was significantly lower than that of the older group. The lower NAA/creatine ratio for the GWS group points to the existence of hippocampal dysfunction.

Noyes, R., Watson, D. B., Carney, C. P., Letuchy, E. M., Peloso, P. M., Black, D. W. et al. (2004). Risk factors for hypochondriacal concerns in a sample of military veterans. *J.Psychosom.Res., 57,* 529-539. (DoD-058, HHS-001)

OBJECTIVE: The aim was to examine the influence of combat exposure and other risk factors on the development of hypochondriacal concerns among veterans of the Gulf War and to learn whether these concerns might be a source of increased symptom reporting among them. METHOD: Six hundred two veterans who were deployed to the Gulf or elsewhere during the 1991 war took part in a two-phase study of symptoms and illnesses occurring among these veterans. Hypochondriacal beliefs and attitudes were assessed by the Whiteley Index and somatic symptoms by a factor-analytically derived measure. Multiple regression models were developed for these outcomes. RESULTS: Hypochondriacal concerns were significantly associated with level of education, personal history of depression, number of prewar physical conditions, family history of functional syndromes, negative and positive temperament and disinhibition, military combat, level of military preparedness, social support, and perceived life stress. Somatic symptoms were associated with these same variables, as well as branch of service, family history of physical conditions, combat, and level of combat exposure. A regression model for hypochondriacal concerns included the number of prewar physical conditions, negative temperament, lack of social support, and perceived life stress. CONCLUSIONS: Hypochondriacal concerns were not strongly related to combat exposure. Consequently, it is not likely that such concerns account for increased symptom reporting among the veterans studied. Hypochondriacal concerns appeared to arise in response to threats posed by physical illness. Vulnerability to such threats appeared to center on the personality dimension of negative temperament. This model may serve as a guide to future investigations.

Orcutt, H. K., Erickson, D. J., & Wolfe, J. (2004). The course of PTSD symptoms among Gulf War veterans: a growth mixture modeling approach. *J.Trauma Stress., 17,* 195-202. (DoD-052 and VA National Center for PTSD)

Relatively little is known about the course of PTSD symptoms over time following trauma exposure. Accordingly, this study utilized a specialized structural equation modeling approach, growth mixture modeling, to examine the trajectory of PTSD symptoms across three time points in a sample of Gulf War veterans (n at Time 1 = 2,949, n at Time 2 = 2,313, and n at Time 3 = 1,327). Results were most consistent with a two-group model suggesting that the course of PTSD symptoms following the Gulf War was best characterized by two distinct growth curves: (1) low levels of PTSD symptoms with little increase over time and (2) higher levels of initial symptoms with a significant increase over time. Thus, it appears that response to Gulf War experiences is not homogeneous, and that a subset of individuals may experience relatively more PTSD symptoms over time. In addition, men, Whites, those reporting more education, and those reporting less combat exposure had a significantly higher probability of being classified into the less symptomatic group.

Strawn, J. R., Ekhator, N. N., Horn, P. S., Baker, D. G., & Geracioti, T. D., Jr. (2004). Blood pressure and cerebrospinal fluid norepinephrine in combat-related posttraumatic stress disorder. *Psychosom.Med., 66,* 757-759.

OBJECTIVE: Central nervous system norepinephrine (NE) is normally involved in blood pressure regulation, but it is pathophysiologically elevated in posttraumatic stress disorder (PTSD). METHODS: We monitored blood pressure while performing serial cerebrospinal fluid (CSF) sampling for 6 hours to determine CSF NE concentrations in men with combat-related PTSD (n = 11) and in healthy men (n = 8). RESULTS: CSF NE concentrations strongly and positively correlated with mean diastolic blood pressure in

the healthy men (R = 0.93, p <.002) but not in the patients (R = 0.10, p =.77). Within individuals, mean arterial pressure, systolic blood pressure, diastolic blood pressure and pulse pressure were poorly correlated over time in patients with PTSD but highly correlated over time in the healthy men, indicating that measurement of these hemodynamic parameters are poorly prognostic of subsequent measurements of the same parameter in patients with PTSD. CONCLUSION: These data demonstrate the loss of the normal direct relationship between CSF NE and blood pressure in combat veterans with PTSD. Whether this dysynchrony mechanistically relates to the hemodynamic abnormalities in PTSD or, like some of the psychobehavioral symptoms, can be corrected with anti-noradrenergic pharmacotherapy remains to be determined.

Thompson, K. E., Vasterling, J. J., Benotsch, E. G., Brailey, K., Constans, J., Uddo, M. et al. (2004). Early symptom predictors of chronic distress in Gulf War veterans. *J.Nerv.Ment.Dis., 192,* 146-152. (VA-012 and National Institutes of Health)
Although there is evidence that specific early hyperarousal, avoidance, and emotional numbing symptoms are associated with later posttraumatic stress disorder (PTSD) symptomatology among veterans, little is known about predictors of later non-PTSD-related psychological symptoms. One and 2 years after serving in the Gulf War, 348 military reservists were assessed for severity of war zone stress, PTSD, psychological distress, and stress-mediated physical complaints. Overall PTSD symptomatology and emotional numbing and hyperarousal symptom clusters increased over time, whereas re-experiencing and avoidance symptoms showed no change. Emotional numbing and hyperarousal symptoms at 1 year predicted generalized distress, depression, anxiety, hostility, and somatic symptoms at 2 years, whereas re-experiencing and avoidance symptoms did not. Findings highlight the importance of targeting early emotional numbing and hyperarousal symptom clusters to reduce longer-term psychological distress.

Environmental Toxicology

The majority of 2004 reports on exposures of Gulf War veterans to potentially toxic agents pertain to depleted uranium, which was used in tank armor and weapons. Findings include no residual exposure in the war theatre (Sztajnkrycer and Otten, 2004) or residue only in dust (Bem and Bou-Rabee, 2004). Veterans with uranium in their bodies were those who had residual shrapnel from ”friendly fire” (Gwiazda et al., 2004; McDiarmid et al., 2004b). Nevertheless, this shrapnel-uranium had no effect on kidney function, site of the presumed greatest effect (McDiarmid et al., 2004a).

Other studies examined the effects (in animals) of neurotoxins that Gulf War veterans may have been exposed to. The opening of the blood-brain barrier in young (but not older) rats by the insecticide paraoxon did not allow for any more than an additive effect of pyridostigmine bromide (Song et al., 2004). Another study involving the effects of sarin, pyridostigmine bromide, and treadmill activity on enzyme activities in mice reported multiple interactions (Husain and Somani, 2004). One report suggested that exposure to pyridostigmine bromide alone or in combination with DEET or permethrin increases binding to a certain type of acetylcholine receptor (Abou-Donia et al., 2004) and might be implicated in sensorimotor deficits (beam walking) in rats. Animals exposed to both stress and chemical agents exhibited a number of neurological changes, including blood-brain barrier disruption and neuronal cell death (Abdel-Rahman et al., 2004). Exposure of animals to low doses of sarin resulted in decreased brain activity (van Helden et al., 2004b) and could evoke non-lethal physiological responses at exposure levels that are not detectable by currently fielded alarm systems (van Helden et al., 2004a).

Abdel-Rahman, A., Abou-Donia, S., El-Masry, E., Shetty, A., & Abou-Donia, M. (2004). Stress and combined exposure to low doses of pyridostigmine bromide, DEET, and permethrin produce neurochemical and neuropathological alterations in cerebral cortex, hippocampus, and cerebellum. *J.Toxicol.Environ.Health A, 67,* 163-192. (DoD-075)
Exposure to a combination of stress and low doses of the chemicals pyridostigmine bromide (PB), DEET, and permethrin in adult rats, a model of Gulf War exposure, produces blood-brain barrier (BBB) disruption and neuronal cell death in the cingulate cortex, dentate gyrus, thalamus, and hypothalamus. In this study, neuropathological alterations in other areas of the brain where no apparent BBB disruption was observed were studied following such exposure. Animals exposed to both stress and chemicals exhibited decreased brain acetylcholinesterase (AChE) activity in the midbrain, brainstem, and cerebellum and decreased m2 muscarinic acetylcholine (ACh) receptor ligand binding in the midbrain and cerebellum. These alterations

were associated with significant neuronal cell death, reduced microtubule-associated protein (MAP-2) expression, and increased glial fibrillary acidic protein (GFAP) expression in the cerebral cortex and the hippocampal subfields CA1 and CA3. In the cerebellum, the neurochemical alterations were associated with Purkinje cell loss and increased GFAP immunoreactivity in the white matter. However, animals subjected to either stress or chemicals alone did not show any of these changes in comparison to vehicle-treated controls. Collectively, these results suggest that prolonged exposure to a combination of stress and the chemicals PB, DEET, and permethrin can produce significant damage to the cerebral cortex, hippocampus, and cerebellum, even in the absence of apparent BBB damage. As these areas of the brain are respectively important for the maintenance of motor and sensory functions, learning and memory, and gait and coordination of movements, such alterations could lead to many physiological, pharmacological, and behavioral abnormalities, particularly motor deficits and learning and memory dysfunction.

Abou-Donia, M. B., Dechkovskaia, A. M., Goldstein, L. B., bdel-Rahman, A., Bullman, S. L., & Khan, W. A. (2004). Co-exposure to pyridostigmine bromide, DEET, and/or permethrin causes sensorimotor deficit and alterations in brain acetylcholinesterase activity. ***Pharmacol.Biochem.Behav., 77,*** **253-262. (DoD-075)**

Military personnel deployed in the Persian Gulf War (PGW) were exposed to a combination of chemicals, including pyridostigmine bromide (PB), DEET, and permethrin. We investigated the dose-response effects of these chemicals, alone or in combination, on the sensorimotor performance and cholinergic system of male Sprague-Dawley rats. Animals were treated with a daily dermal dose of DEET and/or permethrin for 60 days and/or PB (gavage) during the last 15 days. Neurobehavioral performance was assessed on day 60 following the beginning of the treatment with DEET and permethrin. The rats were sacrificed 24 hours after the last treatment for biochemical evaluations. PB alone, or in combination with DEET, or DEET and permethrin resulted in deficits in beam-walk score and longer beam-walk times compared to controls. PB alone, or in combination with DEET, permethrin, or DEET and permethrin caused impairment in incline plane performance and forepaw grip strength. PB alone at all doses slightly inhibited plasma butyryl-cholinesterase activity, whereas combination of PB with DEET or permethrin increased its activity. Brainstem acetylcholinesterase (AChE) activity significantly increased following treatment with combinations of either DEET or permethrin at all doses, whereas the cerebellum showed a significant increase in AChE activity following treatment with a combination of PB/DEET/permethrin. Co-exposure to PB, DEET, and permethrin resulted in significant inhibition in AChE in midbrain. PB alone or in combination with DEET and permethrin at all doses increased ligand binding for m2 muscarinic acetylcholine receptor in the cortex. In addition, PB and DEET together or a combination of PB, DEET, and permethrin significantly increased ligand binding for nicotinic acetylcholine receptor. These results suggest that exposure to various doses of PB, alone and in combination with DEET and permethrin, leads to sensorimotor deficits and differential alterations of the cholinergic system in the central nervous system.

Anthony, J. S., Haley, M., Manthei, J., Way, R., Burnett, D., Gaviola, B. et al. (2004). Inhalation toxicity of Cyclosarin (GF) vapor in rats as a function of exposure concentration and duration: potency comparison to sarin (GB). ***Inhal.Toxicol., 16,*** **103-111. (DoD)**

The inhalation toxicity of cyclohexyl methylphosphonofluoridate (GF) was examined in male and female Sprague-Dawley rats exposed by whole body in a dynamic 750-L chamber. The objectives of this study were to (1) generate GF vapor in a dynamic inhalation chamber system, starting in the lethal to near-lethal concentration range, (2) examine dose-response effects of inhaled GF vapor and analyze the relationship between concentration (C) and exposure duration (T) in determining probability of lethality, and (3) establish a lethal potency ratio between GF and the more volatile agent Sarin (GB). Using a syringe pump, GF vapor concentrations were generated for exposure times of 10, 60, and 240 min. Dose-response curves with associated slopes were determined for each exposure by the Bliss probit method. GF vapor exposures were associated with sublethal clinical signs such as tremors, convulsions, salivation, and miosis. Concentration-exposure time values for lethality in 50% of the exposed population (LCT_{50}) were calculated for 24-h and 14-day postexposure periods for 10-, 60-, and 240-min exposures. In general, LCT_{50} values were lower in female rats than males and increased with exposure duration; that is, CT was not constant over time. The GF LCT_{50} values for female rats were 253 mg min/m^3 at 10 min, 334 mg min/m^3 at 60 min, and 533 mg min/m^3 at 240 min, while the values for males were 371, 396, and 585 mg min/m^3, respectively. The GB LCT_{50} values for female rats were 235 mg min/m^3 at 10 min, 355 mg min/m^3 at 60 min, and 840 mg min/m^3 at 240 min, while the values for males were 316, 433, and 1296 mg min/m^3,

respectively. At longer exposure durations, the LCT_{50} for GF was less than that found for GB but at shorter exposure durations, the LCT_{50} for GF was more than that found for GB. Empirical models, consisting of the toxic load model plus higher order terms, were developed and successfully fit to the data.

Bem, H. & Bou-Rabee, F. (2004). Environmental and health consequences of depleted uranium use in the 1991 Gulf War. *Environ.Int., 30,* 123-134.
Depleted uranium (DU) is a by-product of the 235U radionuclide enrichment processes for nuclear reactors or nuclear weapons. DU in the metallic form has high density and hardness as well as pyrophoric properties, which makes it superior to the classical tungsten armour-piercing munitions. Military use of DU has been recently a subject of considerable concern, not only to radioecologists but also public opinion in terms of possible health hazards arising from its radioactivity and chemical toxicity. In this review, the results of uranium content measurements in different environmental samples performed by authors in Kuwait after Gulf War are presented with discussion concerning possible environmental and health effects for the local population. It was found that uranium concentration in the surface soil samples ranged from 0.3 to 2.5 μg^{-1} with an average value of 1.1 $\mu g\ g^{-1}$, much lower than world average value of 2.8 $\mu g\ g^{-1}$. The solid fallout samples showed similar concentrations varied from 0.3 to 1.7 $\mu g\ g^{-1}$ (average 1.47 $\mu g\ g^{-1}$). Only the average concentration of U in solid particulate matter in surface air equal to 0.24 ng g^{-1} was higher than the usually observed values of approximately 0.1 ng g^{-1} but it was caused by the high dust concentration in the air in that region. Calculated on the basis of these measurements, the exposure to uranium for the Kuwait and southern Iraq population does not differ from the world average estimation. Therefore, the widely spread information in newspapers and Internet (see for example: [CADU NEWS, 2003. http://www.cadu.org.uk/news/index.htm (3-13)]) concerning dramatic health deterioration for Iraqi citizens should not be linked directly with their exposure to DU after the Gulf War.

Bide, R. W. & Risk, D. J. (2004). Inhalation toxicity in mice exposed to sarin (GB) for 20-720 min. *J.Appl.Toxicol., 24,* 459-467. (Defense Research and Development Canada)
Most of the historical data for the toxicity of sarin (GB) was collected for exposure durations of <10 min in attempts to establish the utility of and defense against this agent in offensive military use. However, information concerning the toxicity of GB (and other nerve agents) from longer exposures of 1-12 h is critical for all personnel who must work in or close to low-level concentrations of chemical for extended periods and for all personnel, dressed in Individual Protective Equipment, who need to know when, and if, it is safe to take off these cumbersome garments. The data presented for the toxicity of GB to mice for whole-body exposures of 20 min to 12 h are intended to form part of an ongoing, multi-species effort aimed at establishing toxicity estimates for humans for these longer exposure times: LCT_{50} values of 430, 540, 900, 1210 and 2210 mg min m^{-3} or LC_{50} values of 21.5, 9.0, 5.0, 3.4 and 3.1 mg m^{-3} were obtained for mice for 20-, 60-, 180-, 360- and 720-min exposures to GB, respectively. The data for longer exposures do not follow Haber's rule (LCT_{50}=CT). The 20- and 60-min data fit the 'toxic load model' involving CnT that was established previously from historical data for 0.17-30 min GB exposures to mice. The LCT_{50} and LC_{50} values for 3, 6 and 12 h are progressively higher (toxicity lower) than predicted by either Haber's rule or the toxic load model.

Choi, J., Hodgson, E., & Rose, R. L. (2004). Inhibition of trans-permethrin hydrolysis in human liver fractions by chloropyrifos oxon and carbaryl. *Drug Metabol.Drug Interact., 20,* 233-246. (DoD-103)
Permethrin, a pyrethroid insecticide, is one of several deployment-related chemicals that have been suggested as causative agents for Gulf War related illnesses. Hydrolysis of trans-permethrin (tPMT) is a major route of detoxication and a potential locus for interactions with chemicals with similar use patterns. This study examined the potential inhibitory effects of chlorpyrifos, carbaryl, pyridostigmine bromide and the insect repellent N,N-diethyl-m-toluamide (DEET) on tPMT hydrolysis in human liver fractions. Although chlorpyrifos was not inhibitory, its toxic metabolite, chlorpyrifos oxon, strongly and irreversibly inhibited tPMT hydrolysis at low concentrations (cytosolic and microsomal K_i values of 3 and 16 nM, respectively). Carbaryl, a known anticholinesterase agent, showed non-competitive inhibition kinetics, with K_i values two orders of magnitude higher than those for chlorpyrifos oxon. Although DEET was much less effective than either chlorpyrifos oxon or carbaryl, equimolar concentrations inhibited up to 45% of tPMT hydrolysis. Pyridostigmine bromide showed no inhibitory effects. This study suggests that interaction potential between organophosphorus and pyrethroid insecticides should be considered in safety assessments when both insecticides are deployed simultaneously.

Greenberg, N., Iversen, A. C., Unwin, C., Hull, L., & Wessely, S. (2004). Screening for depleted uranium in the United Kingdom armed forces: who wants it and why? *J.Epidemiol.Community Health, 58,* 558-561. DoD-039 and UK Ministry of Defense)
BACKGROUND: Depleted uranium (DU) use has been implicated in the poor health of many service personnel who have served in the Gulf and the Balkans. Although the health related risks are thought to be small the UK government has offered to set up a voluntary screening programme for service personnel. This study aimed to find out the characteristics and possible exposures to DU for those personnel who desire DU screening. METHODS: This study looks at 2369 UK service personnel who were asked if they wanted to be screened for DU. Subjects were asked about their perceived exposure to deployment associated risks including DU and a number of psychological health measures. RESULTS: The study found that 24% of the cohort wanted screening, a figure that if extrapolated to all those who have been offered screening would represent 36720 requests for screening. Those who wanted DU screening were younger, of lower rank, and more likely to be from the Royal Navy or Army rather than the Royal Air Force. Those requesting DU screening reported poorer health both subjectively and as measured by the GHQ-12 and a symptom checklist. They also reported more exposure to DU and to other deployment associated risks while in military service. Using combat exposure as a proxy for a significant risk of having been exposed to DU, there was a significant correlation. CONCLUSIONS: This study found that the desire for DU screening is more closely linked to current health status rather than plausible exposure to DU.

Gwiazda, R. H., Squibb, K., McDiarmid, M., & Smith, D. (2004). Detection of depleted uranium in urine of veterans from the 1991 Gulf War. *Health Phys., 86,* 12-18. (VA and DoD)
American soldiers involved in "friendly fire" accidents during the 1991 Gulf War were injured with depleted-uranium-containing fragments or possibly exposed to depleted uranium via other routes such as inhalation, ingestion, and/or wound contamination. To evaluate the presence of depleted uranium in these soldiers eight years later, the uranium concentration and depleted uranium content of urine samples were determined by inductively coupled plasma mass spectrometry in (a) depleted uranium exposed soldiers with embedded shrapnel, (b) depleted uranium exposed soldiers with no shrapnel, and (c) a reference group of deployed soldiers not involved in the friendly fire incidents. Uranium isotopic ratios measured in many urine samples injected directly into the inductively coupled plasma mass spectrometer and analyzed at a mass resolution m/delta m of 300 appeared enriched in 235U with respect to natural abundance (0.72%) due to the presence of an interference of a polyatomic molecule of mass 234.81 amu that was resolved at a mass resolution m/delta m of 4,000. The 235U abundance measured on uranium separated from these urines by anion exchange chromatography was clearly natural or depleted. Urine uranium concentrations of soldiers with shrapnel were higher than those of the two other groups, and 16 out of 17 soldiers with shrapnel had detectable depleted uranium in their urine. In depleted uranium exposed soldiers with no shrapnel, depleted uranium was detected in urine samples of 10 out of 28 soldiers. The median uranium concentration of urines with depleted uranium from soldiers without shrapnel was significantly higher than in urines with no depleted uranium, though substantial overlap in urine uranium concentrations existed between the two groups. Accordingly, assessment of depleted uranium exposure using urine must rely on uranium isotopic analyses, since urine uranium concentration is not an unequivocal indicator of depleted uranium presence in soldiers with no embedded shrapnel.

Husain, K. & Somani, S. M. (2004). Persistent/delayed toxic effects of low-dose sarin and pyridostigmine under physical stress (exercise) in mice. *Indian J.Physiol Pharmacol., 48,* 150-164.
Pyridostigmine bromide, a reversible anticholinesterase drug, was used by military personnel during the Gulf War. They were under physical stress and might have been exposed to low-dose nerve gas, sarin. This study examined the interactions of low-dose sarin and pyridostigmine in exercised mice. Male NIH Swiss mice were treated as follows: 1) Control; 2) Sarin (0.01 mg/kg, sc); 3) exercise; 4) sarin plus exercise; 5) pyridostigmine; 6) pyridostigmine plus exercise; 7) pyridostigmine plus sarin; 8) pyridostigmine plus sarin plus exercise. Exercise was given daily for 10 weeks on treadmill and pyridostigmine and sarin were administered daily during the 5th and 6th weeks only. Respiratory exchange ratio decreased significantly during the dosing period of 5th and 6th weeks in groups 4, 6, and 8. Animals were sacrificed 24 hours after the ten-week exercise, tissues isolated and analyzed. Sarin significantly decreased butyrylcholinesterase (BChE) activity in plasma; AChE activity in platelet, triceps muscle, and striatum; neurotoxic esterase (NTE) activity in platelets, spinal cord, cortex and striatum and malondialdehyde (MDA) levels in sciatic nerve and cord. Sarin plus exercise significantly reduced BChE activity in plasma; acetylcholinesterase (AChE) activity in platelets, muscle, nerve and striatum; NTE activity in platelets, cord, cortex and striatum; and increased creatinine phosphokinase (CK) activity in plasma and MDA levels in cord.

Pyridostigmine plus exercise significantly decrease BChE activity in plasma; AChE activity in muscle and enhanced malondialdehyde (MDA) levels in muscle. Pyridostigmine plus sarin significantly decreased NTE activity in platelets, cord, cortex and striatum. Pyridostigmine plus sarin plus exercise significantly altered AChE activity and MDA levels in muscle; and NTE activity in platelets, nerve, cord and cortex. Exercise significantly augmented the changes in plasma CK activity, muscle and nerve AChE activity, platelet NTE activity and cord MDA levels induced by sarin. It is concluded that physical stress (exercise) enhanced the persistent/delayed toxic effects of low-dose sarin and pyridostigmine in specific tissues of mice.

Joaquim, L. F., Farah, V. M., Bernatova, I., Fazan, R., Jr., Grubbs, R., & Morris, M. (2004). Enhanced heart rate variability and baroreflex index after stress and cholinesterase inhibition in mice. ***Am.J.Physiol Heart Circ.Physiol, 287,*** **H251-H257. (DoD)**
Experiments tested the effect of stress coupled with cholinesterase inhibition on blood pressure, heart rate, baroreflex index, and variability in time and frequency domain in conscious mice. The objective was to determine whether cholinergic systems interact with stress to alter cardiovascular responses. Male C57BL/6J mice with arterial catheters were exposed to 3-day treatments: 1) intermittent shaker stress, 2) pyridostigmine (10 $mg.kg^{-1}.day^{-1}$); or 3) combined pyridostigmine and stress. Pyridostigmine reduced blood cholinesterase (-33%) with no added effects of stress. Twenty-four-hour blood pressure recordings showed that there were no differences in blood pressure and heart rate with the treatments. Pulse interval standard deviation was greatly increased in the pyridostigmine/stress group compared with stress or pyridostigmine groups (11.0 +/- 1.4, 5.0 +/- 0.9, and 7.5 +/- 0.9 ms, respectively). Spectral analysis showed two distinct components for pulse interval variability (low and high frequency). Variability in the low-frequency range was greatly enhanced in the pyridostigmine/stress group, seen as a doubling of the power (9.5 +/- 1.7, 3.3 +/- 0.9, and 5.0 +/- 0.6 ms for pyridostigmine/stress, stress and pyridostigmine groups, respectively). Baroreflex sensitivity was also increased in the pyridostigmine/stress group (3.6 +/- 0.5 compared with 1.8 +/- 0.3 and 1.7 +/- 0.5 ms/mmHg in the stress and pyridostigmine groups, respectively). There was no difference in blood pressure variability or its spectral components. Results demonstrate that there are potent interactions between a mild stressor and cholinesterase inhibition seen as an accentuation of low-frequency variability in pulse interval time series, probably associated with baroreflex input and autonomic drive.

McDiarmid, M. A., Engelhardt, S., Oliver, M., Gucer, P., Wilson, P. D., Kane, R. et al. (2004). Health effects of depleted uranium on exposed Gulf War veterans: a 10-year follow-up.
J.Toxicol.Environ.Health A, 67, **277-296. (VA and DoD)**
Medical surveillance of a group of U.S. Gulf War veterans who were victims of depleted uranium (DU) "friendly fire" has been carried out since the early 1990s. Findings to date reveal a persistent elevation of urine uranium, more than 10 yr after exposure, in those veterans with retained shrapnel fragments. The excretion is presumably from ongoing mobilization of DU from fragments oxidizing in situ. Other clinical outcomes related to urine uranium measures have revealed few abnormalities. Renal function is normal despite the kidney's expected involvement as the "critical" target organ of uranium toxicity. Subtle perturbations in some proximal tubular parameters may suggest early although not clinically significant effects of uranium exposure. A mixed picture of genotoxic outcomes is also observed, including an association of hypoxanthine-guanine phosphoribosyl transferase (HPRT) mutation frequency with high urine uranium levels. Findings observed in this chronically exposed cohort offer guidance for predicting future health effects in other potentially exposed populations and provide helpful data for hazard communication for future deployed personnel.

McDiarmid, M. A., Squibb, K., & Engelhardt, S. M. (2004). Biologic monitoring for urinary uranium in gulf war I veterans. ***Health Phys., 87,*** **51-56. (VA and DoD)**
Biologic monitoring for total uranium in urine of Gulf War I veterans concerned about past exposure to depleted uranium (DU) has been offered by the Departments of Veterans Affairs and Defense since the late 1990's. DU, a component of U.S. munitions and tank armor, was first used during that conflict. Two hundred and twenty-seven veterans submitted samples for analysis from January 2000 through December 2002, which included a 24-h urine sample for determination of total urinary uranium concentration and completed questionnaires describing their wartime exposure experiences. Thirty questionnaire items characterizing DU exposure opportunities were collapsed into 19 exposure categories. Urine uranium (U) results were stratified into low and high uranium groups with 0.05 µg U g creatinine as the cut point. Exposure scenarios in the high and low uranium groups were similar in frequency and type with only the presence of retained shrapnel being predictive of a high urine uranium value, as found in the first phase of

this surveillance of 169 veterans performed prior to 2000. Twenty-two veterans exhibited U levels in the high range. Isotopic analysis, available for 21 of these 22, revealed that all but three of these samples contained natural and not depleted uranium. These three participants had retained DU shrapnel as a result of their past injuries. Thus, even with an enlarged cohort, elevated urine uranium values in the absence of retained DU fragments are unlikely. The utility of isotopic analysis to more fully characterize uranium biomonitoring results is also demonstrated.

Song, X., Pope, C., Murthy, R., Shaikh, J., Lal, B., & Bressler, J. P. (2004). Interactive effects of paraoxon and pyridostigmine on blood-brain barrier integrity and cholinergic toxicity. *Toxicol.Sci., 78,* 241-247. (DoD-107)

The effect of the organophosphorous insecticide paraoxon on the integrity of the blood-brain barrier (BBB) and permeability of pyridostigmine (PYR), a peripheral inhibitor of cholinesterase activity, was examined in Long Evans rats. The integrity of the BBB was examined by measuring the number of capillaries leaking horseradish peroxidase, which was injected into the heart. Treatment with 100 µg/kg paraoxon, intramuscularly resulted in a 3- to 4-fold increase in the number of leaky capillaries in young rats (25 to 30 days old) but not in older rats (90 days old). Interestingly, young rats treated with PYR (30 mg/kg, po) 50 min before treatment with paraoxon showed an inhibited effect of paraoxon on the BBB. Furthermore, no increase in the degree of inhibition of acetylcholinesterase activity was observed in young rats treated with PYR before paraoxon compared with young rats treated with paraoxon alone. Cholinergic toxicity, as assessed by changes in behavior, was not observed in young rats treated with paraoxon alone; but, slight signs of cholinergic toxicity were observed in rats treated with PYR. Young rats treated with both PYR and paraoxon did not exhibit more extensive signs of toxicity than rats treated with paraoxon alone or PYR alone. The results indicate that treatment with paraoxon can compromise BBB permeability at dosages that do not induce cholinergic toxicity, but only in young rats. Also, PYR pre-exposure appears to protect the BBB from the paraoxon-induced alterations.

Sztajnkrycer, M. D. & Otten, E. J. (2004). Chemical and radiological toxicity of depleted uranium. *Mil.Med., 169,* 212-216.

A by-product of the uranium enrichment process, depleted uranium (DU) contains approximately 40% of the radioactivity of natural uranium yet retains all of its chemical properties. After its use in the 1991 Gulf War, public concern increased regarding its potential radiotoxicant properties. Whereas in vitro and rodent data have suggested the potential for uranium-induced carcinogenesis, human cohort studies assessing the health effects of natural and DU have failed to validate these findings. Heavy-metal nephrotoxicity has not been noted in either animal studies or Gulf War veteran cohort studies despite markedly elevated urinary uranium excretion. No significant residual environmental contamination has been found in geographical areas exposed to DU. Although continued surveillance of exposed cohorts and environments (particularly water sources) are recommended, current data would support the position that DU poses neither a radiological nor chemical threat.

van Helden, H. P., Trap, H. C., Kuijpers, W. C., Oostdijk, J. P., Benschop, H. P., & Langenberg, J. P. (2004a). Low-level exposure of guinea pigs and marmosets to sarin vapour in air: lowest-observable-adverse-effect level (LOAEL) for miosis. *J.Appl.Toxicol., 24,* 59-68. (DoD-055)

The purpose of this pilot study was to indicate, for low-level exposure of conscious guinea pigs and marmoset monkeys to sarin vapour in air, the lowest-observable-adverse-effect level (LOAEL) of sarin for miosis. This is the concentration x time (C.t) value (t = 5 h) of exposure at which miosis becomes significant. The ratio of pupil and iris diameters, measured on digital photographs taken on-line during exposure, was calculated as a measure for miosis. The exposure concentrations were in the range 7-150 µg x m^{-3} and the exposure times needed to achieve significant miosis were in the range 10-300 min. Both vehicle- and pyridostigmine-pretreated animals were used in the experiments. The latter pretreatment resulted in ca. 30% inhibition of erythrocyte acetylcholinesterase in both species. In vehicle-pretreated guinea pigs and marmosets the pupil size was decreased significantly ($P < 0.05$) at sarin doses of 1.8 +/- 0.3 and 2.5 +/- 0.8 mg x min x m^{-3}, respectively. In pyridostigmine-pretreated guinea pigs and marmosets the pupil size was affected significantly ($P < 0.05$) at 1.8 +/- 0.5 and 3.0 +/- 0.8 mg x min x m^{-3}, respectively. Evidently there is no significant influence of pyridostigmine pretreatment on the LOAEL. These data were addressed in light of the recommended occupational and detection limits for sarin vapour in air. It was concluded that miosis will occur during low-level sarin exposure at levels that are not detectable by the currently fielded alarm systems, assuming that humans are as sensitive for sarin vapour in air as guinea pigs and marmosets.

van Helden, H. P., Vanwersch, R. A., Kuijpers, W. C., Trap, H. C., Philippens, I. H., & Benschop, H. P. (2004b). Low levels of sarin affect the EEG in marmoset monkeys: a pilot study. *J.Appl.Toxicol., 24,* 475-483. (DoD-055)
The main purpose of this pilot study was to estimate the lowest observable adverse effect level (LOAEL) for the electroencephalogram (EEG) upon long-term, low-level exposure of vehicle-pretreated and pyridostigmine-pretreated marmoset monkeys to sarin vapour. This is the C.t value (t=5 h) of exposure at which the EEG becomes significantly different from that resulting from air exposure of the same animals. The LOAELs for effects on the EEG in vehicle- and pyridostigmine-pretreated marmosets appeared to be 0.2 and 0.1 mg min m^3, respectively. Comparatively, the latter LOAEL values are at least an order of magnitude lower than the previously established LOAEL for miosis and only 2-5 times higher than the lowest observable effect level of bound sarin in blood. The second aim of the study was to analyze the EEG of the same marmosets again during a 5-h exposure to air 1 year after exposure to sarin vapour. All the marmosets still demonstrated significant ($P < 0.05$) EEG differences. In most vehicle-pretreated marmosets the energy (microV2) per EEG band was higher than that observed 1 year earlier, which might indicate that neurons had become more sensitive to excitation. This phenomenon was less pronounced in pyridostigmine-pretreated animals. Visual examination of the EEG records revealed clear bursts of alpha frequencies (ca. 9 Hz), resembling sleep-spindles, that were present more frequently in both groups of exposed marmosets than in naive animals. These late changes in spindle oscillation might be the result of changes in the cholinergic system due to exposure to sarin vapour 1 year previously. In conclusion, EEG abnormalities persisting for more than 1 year may occur in humans during long-term (5 h) exposure to subclinical levels of sarin that are not detectable by the currently fielded alarm systems.

Westphal, C. S., McLean, J. A., Hakspiel, S. J., Jackson, W. E., McClain, D. E., & Montaser, A. (2004). Determination of depleted uranium in urine via isotope ratio measurements using large-bore direct injection high efficiency nebulizer-inductively coupled plasma mass spectrometry. *Appl.Spectrosc., 58,* 1044-1050.
Inductively coupled plasma mass spectrometry (ICP-MS), coupled with a large-bore direct injection high efficiency nebulizer (LB-DIHEN), was utilized to determine the concentration and isotopic ratio of uranium in 11 samples of synthetic urine spiked with varying concentrations and ratios of uranium isotopes. Total U concentrations and $^{235}U/^{238}U$ isotopic ratios ranged from 0.1 to 10 μg/L and 0.0011 and 0.00725, respectively. The results are compared with data from other laboratories that used either alpha-spectrometry or quadrupole-based ICP-MS with a conventional nebulizer-spray chamber arrangement. Severe matrix effects due to the high total dissolved solid content of the samples resulted in a 60 to 80% loss of signal intensity, but were compensated for by using ^{233}U as an internal standard. Accurate results were obtained with LB-DIHEN-ICP-MS, allowing for the positive identification of depleted uranium based on the $^{235}U/^{238}U$ ratio. Precision for the $^{235}U/^{238}U$ ratio is typically better than 5% and 15% for ICP-MS and alpha-spectrometry, respectively, determined over the concentrations and ratios investigated in this study, with the LB-DIHEN-ICP-MS system providing the most accurate results. Short-term precision (6 min) for the individual ^{235}U and ^{238}U isotopes in synthetic urine is better than 2% (N = 7), compared to approximately 5% for conventional nebulizer-spray chamber arrangements and >10% for alpha-spectrometry. The significance of these measurements is discussed for uranium exposure assessment of Persian Gulf War veterans affected by depleted uranium ammunitions.

Immune Function and Infectious Diseases

Reports published in 2004 in the area of immune function and infectious diseases focused mainly on the prevalence of altered immune function or host defense mechanisms in Gulf War veterans as related to the presence or absence of exposure.

Two separate case-controlled studies reported altered immune functions in Gulf War veterans. The first (Skowera et al., 2004) reported an increased Th1-type (pro-inflammatory) immune activation in symptomatic Gulf War veterans compared with the control group, with a significant increase in interferon-γ levels and a biased generation of memory cells secreting the cytokine IL-10. The second study (Vojdani and Thrasher, 2004) reported a significant increase over controls in the percentage of antibody-producing B cells in Gulf War veterans, as well as a significantly higher level of antibodies to the person's own myelin basic protein and striated smooth muscle in the test group. Two other reports observed elevated Th1 responses leading to autoimmune responses (Staines, 2004b; Staines, 2004a). In one report, the possibility

that an autoimmune response to a neuropeptide may develop due to possible molecular mimicry with a sandfly protein was discussed. In the second, a biologically plausible mechanism for the development of osteoporosis based on the loss of immune tolerance to a vasoactive calcitonin-related neuropeptide was described. The first study to examine the immunotoxicological effects of pyridostigmine bromide (Peden-Adams et al., 2004) showed that in a mouse model, the compound selectively suppressed humoral antibody responses. A randomized double-blind, placebo-controlled clinical trial of treatment with the antibiotic doxycycline was carried out to determine if mycoplasma infection was a contributing factor or cause of ill Gulf War veterans' symptoms; no statistically significant differences were found between the doxycycline and placebo groups (Donta et al., 2004). A related report addressed the effectiveness of mass mailing and direct telephone contacts in recruitment of veterans into the antibiotic treatment randomized clinical trial (Resio et al., 2004).

Donta, S. T., Engel, C. C., Jr., Collins, J. F., Baseman, J. B., Dever, L. L., Taylor, T. et al. (2004). Benefits and harms of doxycycline treatment for Gulf War veterans' illnesses: a randomized, double-blind, placebo-controlled trial. *Ann.Intern.Med., 141,* 85-94. (DoD-119, VA-055, and Pfizer Pharmaceuticals)

BACKGROUND: It has been hypothesized that certain Mycoplasma species may cause Gulf War veterans' illnesses (GWVIs), chronic diseases characterized by pain, fatigue, and cognitive symptoms, and that affected patients may benefit from doxycycline treatment. OBJECTIVE: To determine whether a 12-month course of doxycycline improves functional status in Gulf War veterans with GWVIs. DESIGN: A randomized, double-blind, placebo-controlled clinical trial with 12 months of treatment and 6 additional months of follow-up. SETTING: 26 U.S. Department of Veterans Affairs and 2 U.S. Department of Defense Medical Centers. PARTICIPANTS: 491 deployed Gulf War veterans with GWVIs and detectable Mycoplasma DNA in the blood. INTERVENTION: Doxycycline, 200 mg, or matching placebo daily for 12 months. MEASUREMENTS: The primary outcome was the proportion of participants who improved more than 7 units on the Physical Component Summary score of the Veterans Short Form-36 General Health Survey 12 months after randomization. Secondary outcomes were measures of pain, fatigue, and cognitive function and change in positivity for Mycoplasma species at 6, 12, and 18 months after randomization. RESULTS: No statistically significant differences were found between the doxycycline and placebo groups for the primary outcome measure (43 of 238 participants [18.1%] vs. 42 of 243 participants [17.3%]; difference, 0.8 percentage point [95% CI, -6.5 to 8.0 percentage points]; $P > 0.2$) or for secondary outcome measures at 1 year. In addition, possible differences in outcomes at 3 and 6 months were not apparent at 9 or 18 months. Participants in the doxycycline group had a higher incidence of nausea and photosensitivity. LIMITATIONS: Adherence to treatment after 6 months was poor. CONCLUSION: Long-term treatment with doxycycline did not improve outcomes of GWVIs at 1 year.

Peden-Adams, M. M., Dudley, A. C., EuDaly, J. G., Allen, C. T., Gilkeson, G. S., & Keil, D. E. (2004). Pyridostigmine bromide (PYR) alters immune function in B6C3F1 mice. *Immunopharmacol.Immunotoxicol., 26,* 1-15. (DoD-076)

Pyridostigmine bromide (PYR) is an anticholinesterase drug indicated for the treatment of myasthenia gravis and neuromuscular blockade reversal. It acts as a reversible cholinesterase inhibitor and was used as a pretreatment for soldiers during Operation Desert Storm to protect against possible nerve gas attacks. Since that time, PYR has been implicated as a possible causative agent contributing to Gulf War Illness. PYR's mechanism of action has been well-delineated with regards to its effects on the nervous system, yet little is known regarding potential effects on immunological function. To evaluate the effects of PYR on immunological function, adult female B6C3F1 mice were gavaged daily for 14 days with PYR (0, 1, 5, 10, or 20 mg/kg/day). Immune parameters assessed were lymphoproliferation, natural killer cell activity, the SRBC-specific antibody plaque-forming cell (PFC) response, thymus and spleen weight and cellularity, and thymic and splenic CD4/CD8 lymphocyte subpopulations. Exposure to PYR did not alter splenic and thymus weight or splenic cellularity. However, 20 mg PYR/kg/day decreased thymic cellularity with decreases in both CD4+/CD8+ (20 mg/kg/day) and CD4-/CD8- (10 and 20 mg/kg/day) cell types. Functional immune assays indicated that lymphocyte proliferative responses and natural killer cell activity were normal; whereas exposure to PYR significantly decreased primary IgM antibody responses to a T-cell dependent antigen at the 1, 5, 10 and 20 mg/kg treatment levels for 14 days. This is the first study to examine the immunotoxicological effects of PYR and demonstrate that this compound selectively suppresses humoral antibody responses.

Resio, M. A., Baltch, A. L., & Smith, R. P. (2004). Mass mailing and telephone contact were effective in recruiting veterans into an antibiotic treatment randomized clinical trial. *J.Clin.Epidemiol., 57,* 1063-1070. (VA-055, DoD-119)

OBJECTIVE: Achieving enrollment goals of randomized clinical trials (RCT) within budgets depends on the timely recruitment of sufficient numbers of participants. We report a comparison of recruitment methods and yields of previously deployed veterans into a large RCT. STUDY DESIGN AND SETTING: A retrospective survey concerning recruitment was administered to staff at 28 sites participating in the VA Cooperative Study #475, "Antibiotic Treatment of Gulf War Veterans' Illnesses" (GWVI). RESULTS: Twenty-one sites reported identifying 31,407 Gulf War Veterans (GWV). Of these, 13.7% were successfully contacted, 3.5% were enrolled, and 1.2% were randomized. Mass mailings and direct telephone calls to GWV identified from a GWV database accounted for 78% of the GWV contacted. The other 22% were contacted by using referrals from medical staff, veterans' groups, media advertisements, and other methods. Data collected prospectively at the Albany Stratton VAMC were similar to data collected retrospectively from other sites. CONCLUSION: These findings demonstrate that in previously deployed GWV with GWVI, 1.2% could be randomized. Although the use of all recruitment methods combined achieved the study recruitment goal, these data demonstrate that mass mailing and direct telephone contacts were effective recruitment methods.

Skowera, A., Hotopf, M., Sawicka, E., Varela-Calvino, R., Unwin, C., Nikolaou, V. et al. (2004). Cellular immune activation in Gulf War veterans. *J.Clin.Immunol., 24,* 66-73. (DoD-106 and UK Medical Research Council)

The etiology and pathology of illnesses related to the first Persian Gulf War are unclear. Among the constellation of symptoms noted in sick veterans, some, such as skin rashes, musculoskeletal pains, and neuropsychiatric problems, have been proposed to reflect an underlying immune dysfunction. In this study we explored the hypothesis that sickness following deployment to the Gulf in 1991 is associated with altered immune function, and we examine possible associated exposures. In particular, we focused on peripheral blood Th1/Th2 balance by measuring intracellular production of IFN-γ, IL-2 (Th1), IL-4 (Th2), and IL-10 by CD4 T cells, using a nested case control study design within a large epidemiological survey. We compared symptomatic Gulf War veterans (sGWV) with well GWVs (wGWV) and a second control group of symptomatic veterans who served in Bosnia or were non-deployed military personnel of the same era. We found evidence for an altered immune status in sGWV in comparison to the other study groups. In particular, ongoing Th1-type immune activation was associated with multisymptom illness in GWVs, with sick veterans having significantly elevated levels of IFN-γ and IL-2 producing CD4+ cells in the absence of in vitro stimulation compared with wGWVs ($P = 0.01$ and $P = 0.001$). In vitro polyclonal activation revealed significantly elevated levels of IL-10 producing memory CD4 cells in sGWVs ($P < 0.001$), but other cytokines were normal. In terms of possible exposures that might influence immune function, we found a trend for reduced levels of IFN-γ producing cells after polyclonal activation with increasing numbers of vaccines administered ($P < 0.05$) but no changes in other cytokines. These data show that multisymptom illness in Gulf War veterans is characterized by ongoing Th1-type immune activation and a biased generation of memory cells secreting the suppressor cytokine, IL-10.

Staines, D. R. (2004a). Is Gulf War Syndrome an autoimmune disorder of endogenous neuropeptides, exogenous sandfly maxadilan and molecular mimicry? *Med.Hypotheses, 62,* 658-664.

Gulf War Syndrome (GWS) remains a contentious diagnosis with conflicting laboratory investigation and lack of a biologically plausible aetiology. This paper discusses the potential role of maxadilan, a potent sandfly vasoactive peptide, in causing autoimmune responses in susceptible individuals through possible molecular mimicry with pituitary adenylate cyclase activating polypeptide (PACAP) and the PAC1R receptor. Gulf War Syndrome may share some causative pathology with Chronic Fatigue Syndrome (CFS), a disorder characterized by prolonged fatigue and debility mostly associated with post-infection sequelae although ongoing infection is unproven. Immunological aberration associated with an expanding group of vasoactive neuropeptides in the context of molecular mimicry and inappropriate immunological memory has been recently raised as possible cause of CFS. Vasoactive neuropeptides act as hormones, neurotransmitters, immune modulators and neurotrophes. They are readily catalysed to small peptide fragments. They and their binding sites are immunogenic and are known to be associated with a range of autoimmune conditions. Maxadilan, while not sharing substantial sequence homology with PACAP is a known agonist of the PACAP specific receptor (PAC1R) and therefore emulates these functions. Moreover a specific amino acid sequence peptide deletion within maxadilan converts it to a PACAP receptor antagonist raising the possibility of this substance provoking a CFS like response in humans exposed to it.

This paper describes a biologically plausible mechanism for the development of a GWS-like chronic fatigue state based on loss of immunological tolerance to the vasoactive neuropeptide PACAP or its receptor following bites of the sandfly Phlebotomus papatasi and injection of the vasodilator peptide maxadilan. Exacerbation of this autoimmune response as a consequence of recent or simultaneous multiple vaccination exposures deserves further investigation. While the possible association between the relatively recently discovered vasoactive neuropeptides and chronic fatigue conditions has only recently been reported in the literature, this paper explores links for further research into GWS and CFS.

Staines, D. R. (2004b). Is osteoporosis linked to vaccinations and Gulf War Syndrome? *Med.Hypotheses, 62,* 670-673.
Gulf War Syndrome (GWS) remains a contentious diagnosis with conflicting laboratory investigations and lack of a biologically plausible aetiology. Assertions have been made that GWS may be the result of vaccinations given to serving military personnel in the Persian Gulf and may be associated with osteoporosis. Calcitonin gene related protein (CGRP) is a vasoactive neuropeptide that is synthesised in conjunction with calcitonin gene expression. Vasoactive neuropeptides act as hormones, neurotransmitters, immune modulators and neurotrophes. They are readily catalysed to small peptide fragments. They and their binding sites are immunogenic and are known to be associated with a range of autoimmune conditions. This paper describes a biologically plausible mechanism for the development of osteoporosis in the context of GWS based on loss of immunological tolerance to the vasoactive neuropeptide CGRP or its receptors following a variety of antigenic events.

Vojdani, A. & Thrasher, J. D. (2004). Cellular and humoral immune abnormalities in Gulf War veterans. *Environ.Health Perspect., 112,* 840-846.
We examined 100 symptomatic Gulf War veterans (patients) and 100 controls for immunologic assays. The veterans and controls were compared for the percentage of T cells (CD3); B cells (CD19); helper:suppressor (CD4:CD8) ratio; natural killer (NK) cell activity; mitogenic response to phytohemagglutin (PHA) and pokeweed mitogen (PWM); level of immune complexes; myelin basic protein (MBP) and striated and smooth muscle autoantibodies; and antibodies against Epstein-Barr virus, cytomegalovirus, herpes simplex virus type 1 (HSV-1), HSV-2, human herpes Type 6 (HHV-6), and Varicella zoster virus (VZV). The percentage of T cells in patients versus controls was not significantly different, whereas a significantly higher proportion of patients had elevated T cells compared with controls. The percentage of B cells was significantly elevated in the patients versus the controls. The NK cell (NK) activity was significantly decreased in the patients (24.8 +/- 16.5 lytic units) versus the controls (37.3 +/- 26.4 lytic units). The percentage of patients with lower than normal response to PHA and PWM was significantly different from controls. Immune complexes were significantly increased in the patients (53.1 +/- 18.6, mean +/- SD) versus controls (34.6 +/- 14.3). Autoantibody titers directed against MBP and striated or smooth muscle were significantly greater in patients versus controls. Finally, the patients had significantly greater titers of antibodies to the viruses compared with the controls ($p < 0.001$). These immune alterations were detected 2-8 years after participation in the Gulf War. The immune alterations are consistent with exposure to different environmental factors. We conclude that Gulf War syndrome is a multifaceted illness with immune function alterations that may be induced by various factors and are probably associated with chronic fatigue syndrome.

Reproductive Health

In 2004, there were four publications about the impact of the Gulf War on reproductive problems and birth defects. Two studies reported on the outcome of pregnancies of female Gulf War veterans. One study suggested that the outcome of Gulf War-exposed conceptions and non-deployed conceptions had similar outcomes, but the Gulf War veterans' postwar conceptions were at increased risk for ectopic pregnancies and spontaneous abortions (Araneta et al., 2004). The second paper, a study of United Kingdom veterans, found no evidence of an association between risk of miscarriage and mothers' service in the Gulf War (Doyle et al., 2004). The same study reported an association between fathers' service in the Gulf War and an increased risk of miscarriage and possibly malformations. According to one report, there may be an association between service in the Gulf War and male infertility (Maconochie et al., 2004). A study by Haddad and co-workers (Haddad et al., 2004) concluded that the majority of infertile males in their group had a low sperm count, and since the Gulf War, there was no major change in testicular cytology numbers.

Abushaban, L., Al-Hay, A., Uthaman, B., Salama, A., & Selvan, J. (2004). Impact of the Gulf war on congenital heart diseases in Kuwait. *Int.J.Cardiol., 93,* 157-162.
BACKGROUND: There has been concern over the increase in the number of babies born with congenital heart diseases (CHD) in Kuwait after the Gulf War. METHODS: We evaluated retrospectively the number of Kuwaiti infants who were diagnosed to have CHD within the first year of life. The comparison was made between those presented from January 1986 to December 1989 (preinvasion) and those presented after the liberation of Kuwait (from January 1992 to December 2000).The number of cases was considered per 10,000 live births in that year. RESULTS: The numbers of cases were 2704 (326 before the invasion and 2378 after liberation). The mean annual incidence of CHD was 39.5 and 103.4 (per 10,000 live births) before and after the Gulf War, respectively (P<0.001). There was an increase in the number of babies with CHD during the immediate 3 years postliberation with a relative reduction in the trend from 1995 to 2000, in some types of CHD. CONCLUSIONS: In our series, there was an increased incidence of CHD almost immediately following the end of the Gulf War period. The cause of this increase remains relatively obscure. Environmental pollution may be a contributing factor; others such as possible psychological trauma remain subject to speculation.

Araneta, M. R., Kamens, D. R., Zau, A. C., Gastanaga, V. M., Schlangen, K. M., Hiliopoulos, K. M. et al. (2004). Conception and pregnancy during the Persian Gulf War: the risk to women veterans. *Ann.Epidemiol., 14,* 109-116. (DoD-001D)
PURPOSE: To enumerate Gulf-War (GW) exposed conceptions and to compare reproductive outcomes of GW-exposed pregnancies with postwar conceptions of women Gulf War veterans (GWV) and women non-deployed veterans (NDV). METHODS: Deployment data and inpatient records from 153 military hospitals identified servicewomen who were pregnant between August 1990 and May 1992 and belonged to military units that were deployed to the Gulf War. Postal surveys were used in 1997 and 1998 to elicit reproductive history; responses were validated against military hospitalization records. Reproductive outcomes of GW-exposed pregnancies were compared with postwar conceptions of women GWVs and NDVs. RESULTS: 3285 women had a pregnancy-related admission; of these, 1558 completed the questionnaire. Self-reported reproductive outcomes and dates, gestational data, and individual deployment dates identified 415 Gulf War-exposed pregnancies, 298 GWV postwar conceptions, and 427 NDV conceptions. Compared with NDV conceptions, adverse reproductive outcomes were similar among GW-exposed pregnancies. However, spontaneous abortions [NDV: 9.1%, GWV postwar: 22.8%, adjusted odds ratio (OR) = 2.92, 95% confidence interval (CI): 1.9, 4.6] and ectopic pregnancies (NDV: 1.4%, GWV postwar: 10.7%, adjusted OR=7.70, 95% CI, 3.0, 20) were elevated for GWV postwar conceptions. CONCLUSION: GW-exposed conceptions and non-deployed conceptions had similar outcomes. However, GWV postwar conceptions were at increased risk for ectopic pregnancies and spontaneous abortions.

Doyle, P., Maconochie, N., Davies, G., Maconochie, I., Pelerin, M., Prior, S. et al. (2004). Miscarriage, stillbirth and congenital malformation in the offspring of UK veterans of the first Gulf war. *Int.J.Epidemiol., 33,* 74-86. (UK Ministry of Defense)
OBJECTIVES: To assess whether the offspring of UK veterans of the first Gulf War are at increased risk of fetal death or congenital malformation. METHOD: This was a retrospective reproductive cohort study comparing UK Gulf War veterans and a demographically similar comparison group who were in service at the time but not deployed to the Gulf. Reproductive history was collected by means of a validated postal questionnaire between 1998 and 2001. RESULTS: In all, 27 959 pregnancies reported by men and 861 pregnancies reported by women were conceived after the first Gulf War and before November 1997. The risk of reported miscarriage was higher among pregnancies fathered by Gulf War veterans than by non-Gulf War veterans (OR = 1.4, 95% CI: 1.3, 1.5). Stillbirth risk was similar in both groups. Male Gulf war veterans reported a higher proportion of offspring with any type of malformation than the comparison cohort (OR = 1.5, 95% CI: 1.3, 1.7). Examination by type of malformation revealed some evidence for increased risk of malformations of the genital system, urinary system (renal and urinary tract), and 'other' defects of the digestive system, musculoskeletal system, and non-chromosomal (non-syndrome) anomalies. These associations were weakened when analyses were restricted to clinically confirmed conditions. There was little or no evidence of increased risk for other structural malformations, specific syndromes, and chromosomal anomalies. Among female veterans, no effect of Gulf War service was found on the risk of miscarriage. The numbers of stillbirths and malformations reported by women were too small to allow meaningful analyses. CONCLUSION: We found no evidence for a link between paternal deployment to the Gulf War and increased risk of stillbirth, chromosomal malformations, or congenital syndromes. Associations were found between fathers' service in the Gulf War and increased risk of miscarriage and less

well-defined malformations, but these findings need to be interpreted with caution as such outcomes are susceptible to recall bias. The finding of a possible relationship with renal anomalies requires further investigation. There was no evidence of an association between risk of miscarriage and mothers' service in the Gulf.

Haddad, F. H., Omari, A. A., Malkawi, O. M., Ajour, W. K., Izat, A., Khasrof, H. et al. (2004). Patterns of testicular cytology in men with primary infertility: any change since the Gulf War? *Acta Cytol., 48,* 807-812.
OBJECTIVE: To evaluate the patterns of testicular cytology in men with primary infertility, to compare the morphologic patterns between the periods 1990-1995, immediately after Gulf War II, and 1997-2001 and to determine whether there is a correlation between hormonal profile, testicular volume and morphologic pattern. STUDY DESIGN: Retrospective study of men with primary infertility. History, complete physical examination, hormonal assay and testicular ultrasound were evaluated. A total of 545 patients had samples for testicular cytology obtained from both testes. The patient's consent was obtained in all cases. Smears were interpreted under light microscopy after treatment with Diff-Quik. A total of 104 healthy, fertile subjects were used for comparison of the hormonal profile and testicular volume. RESULTS: The mean (+/- SD) age was 28.66 +/- 4.36 years and duration of marriage 4.4 +/- 4.36 years. There were 11.2% patients with normal cytology, 55.8% with hypospermatogenesis, 28.4% with testicular atrophy, 2.9% with Sertoli cells only and 1.7% with maturation arrest. A significant increase in hypospermatogenesis and decrease in the Sertoli cell-only pattern were noted in 1997-2001 when compared with 1990-1995. The mean left testicular volume was 10.53 +/- 5.51 mL3 in the infertile group vs. 15.2 +/- 4.97 in the fertile group ($p < 0.003$); right testicular volume was 10.84 +/- 4.77 vs. 15.15 +/- 5.31 ($p < 0.003$). The hormonal profile revealed higher luteinizing hormone and follicle-stimulating hormone levels in the infertile group vs. control group (8.53 +/- 9.03 and 16.44 +/- 19.243 vs. 6.98 +/- 4.53 and 7.37 +/- 6.63, respectively [$p < 0.001$]). Free testosterone was higher in the fertile group (39.69 +/- 12.76 vs. 20.28 +/- 8.5 [$p < 0.000$]). CONCLUSION: The majority of infertile males in our cohort had hypospermatogenesis; testicular atrophy was the next most common disorder. There was no major change in overall absolute numbers since the Gulf War. Testicular cytology by fine needle aspiration is a safe and well-tolerated complementary investigation for unexplained male infertility.

Maconochie, N., Doyle, P., & Carson, C. (2004). Infertility among male UK veterans of the 1990-1 Gulf war: reproductive cohort study. *BMJ, 329,* 196-201. (UK Ministry of Defense)
OBJECTIVES: To examine the hypothesis that, theoretically at least, exposure to toxicants of the type present in the Gulf War could affect spermatogenesis, which might be observed as increased levels of infertility. DESIGN: Retrospective reproductive cohort analysis. SETTING: Male UK Gulf War veterans and matched comparison group of non-deployed servicemen, surveyed by postal questionnaire. PARTICIPANTS: 42,818 completed questionnaires were returned, representing response rates of 53% for Gulf veterans and 42% for non-Gulf veterans; 10,465 Gulf veterans and 7376 non-Gulf veterans reported fathering or trying to father pregnancies after the Gulf War. MAIN OUTCOME MEASURES: Failure to achieve conceptions (type I infertility) or live births (type II infertility) after the Gulf war, having tried for at least a year and consulted a doctor; time to conception among pregnancies fathered by men not reporting fertility problems. RESULTS: Risk of reported infertility was higher among Gulf War veterans than among non-Gulf veterans (odds ratio for type I infertility 1.41, 95% confidence interval 1.05 to 1.89; type II 1.50, 1.18 to 1.89). This small effect was constant over time since the war and was observed whether or not the men had fathered pregnancies before the war. Results were similar when analyses were restricted to clinically confirmed diagnoses. Pregnancies fathered by Gulf veterans not reporting fertility problems also took longer to conceive (odds ratio for > 1 year 1.18, 1.04 to 1.34). CONCLUSIONS: We found some evidence of an association between Gulf War service and reported infertility. Pregnancies fathered by Gulf veterans with no fertility problems also reportedly took longer to conceive.

Symptoms and General Health Status

Several investigations relating symptoms to Gulf War military service were published in 2004. These studies suggest that a variety of symptoms are more common and more severe in Gulf War veterans than in veterans not deployed to the Gulf (Ferguson et al., 2004b; Forbes et al., 2004b; Gray et al., 2004b; Kelsall et al., 2004a; Simmons et al., 2004; Smith et al., 2004), and are also more severe than in patients with sporadic chronic fatigue syndrome (Kennedy et al., 2004). Persistence of symptoms is significantly

influenced by psychological stress (Hotopf et al., 2004), and the symptoms do not cluster in a manner that provides support for the existence of a unique "Gulf War illness" (Engel et al., 2004; Forbes et al., 2004a; Gray et al., 2004a; Nisenbaum et al., 2004; Richardson and Engel, Jr., 2004).

One study reported an association of an angiotensin-converting enzyme (ACE) gene polymorphism with medically unexplained symptoms in Gulf War veterans (Vladutiu and Natelson, 2004), while another noted possible associations of several gene polymorphisms with multiple chemical sensitivity (McKeown-Eyssen et al., 2004). Neither study was designed in a manner that enables definitive testing of these hypotheses. Odors and sounds are triggers for medically unexplained symptoms, with the intensity of the odor or duration of sound positively associated with the severity of the symptoms (Ferguson et al., 2004a). Diesel vapor exposure was also found to trigger symptoms of disorientation, dizziness, respiratory discomfort, and general malaise (Fiedler et al., 2004).

In the area of chronic fatigue, cholinergic abnormalities were found in veterans with "chronic fatigue syndrome" that were not present in veterans with "Gulf War syndrome" (Khan et al., 2004). Although Natelson (Natelson, 2004) suggests other causative factors to fatigue besides stress, a study done in the UK (Rose et al., 2004) suggests that in veterans with more than four neuromuscular symptoms, actual fatigue does not correlate with self-perception of weakness or fatigue, positive muscle biopsies, or abnormal enzyme activities. A study of ill Gulf War veterans showed a blunting of the normal variations in heart rate and concluded that some symptoms in Gulf War veterans may be due to subtle autonomic nervous system dysfunction (Haley et al., 2004).

Two papers published in 2004 reported on respiratory problems in Gulf War veterans. The authors of one paper reported that their findings did not support the theory that the 1990-1991 Gulf War deployment resulted in an increase in lung abnormalities 10 years later (Karlinsky et al., 2004). A study of Australian Gulf War veterans found that they had a higher than expected prevalence of respiratory symptoms and conditions, but they did not have poorer lung function or abnormalities compared to the control group (Kelsall et al., 2004b).

A number of papers examined the health consequences of the anthrax vaccine. One of these specifically addressed the validity of self-reporting and the extent of a reporting bias in evaluation of health consequences of anthrax vaccination (Mahan et al., 2004).

Binder, L. M. & Campbell, K. A. (2004). Medically unexplained symptoms and neuropsychological assessment. *J.Clin.Exp.Neuropsychol., 26,* 369-392. (VA-006)
Several illnesses expressed somatically that do not have clearly demonstrated pathophysiological origin and that are associated with neuropsychological complaints are reviewed. Among them are nonepileptic seizures, fibromyalgia, chronic fatigue syndrome, Persian Gulf War unexplained illnesses, toxic mold and sick building syndrome, and silicone breast implant disease. Some of these illnesses may be associated with objective cognitive abnormalities, but it is not likely that these abnormalities are caused by traditionally defined neurological disease. Instead, the cognitive abnormalities may be caused by a complex interaction between biological and psychological factors. Nonepileptic seizures serve as an excellent model of medically unexplained symptoms. Although nonepileptic seizures clearly are associated with objective cognitive abnormalities, they are not of neurological origin. There is evidence that severe stressors and PTSD are associated with immune system problems, neurochemical changes, and various diseases; these data blur the distinctions between psychological and organic etiologies. Diagnostic problems are intensified by the fact that many patients are poor historians. Patients are prone to omit history of severe stressors and psychiatric problems, and the inability to talk about stressors increases the likelihood of suffering from physiological forms of stress.

Brewer, N. T., Hallman, W. K., Fiedler, N., & Kipen, H. M. (2004). Why do people report better health by phone than by mail? *Med.Care, 42,* 875-883. VA-005A and HHS-006)
CONTEXT: Past research shows that fewer health symptoms are reported by phone than by mail. OBJECTIVES: We sought to examine whether interview mode-dependent differences in health symptom reporting are the result of socially desirable responding or to expending less cognitive effort when formulating responses, a behavior known as satisficing. DESIGN: Participants were randomly assigned to telephone interview only or to mail interview followed 2 weeks later by telephone interview. SETTING &

PARTICIPANTS: Participants were American veterans from the Gulf War Registry (n=719). MAIN OUTCOME MEASURES: Our main outcome measure was the number of mild, moderate, or severe symptoms reported (of 48 possible). RESULTS: Veterans reported an average of 5 more symptoms via mail than via telephone, $F(1, 709) = 32.50$, $P < 0.001$. The difference was mainly the result of symptoms reported by mail as mild but not reported at all by phone. Veterans with higher social desirability scores reported fewer symptoms by phone and mail, $F(1, 709) = 10.11$, $P = 0.001$, but social desirability scores did not interact with interview mode. Furthermore, embarrassing symptoms such as genital complaints were no less likely to be reported by phone. CONCLUSIONS: Reporting of better health in phone surveys is the result of fewer mild symptoms reports but not of socially desirable responding. The findings are consistent with phone interviews encouraging satisficing by limiting the recall of less severe health states. Researchers should handle mild symptom reports with some skepticism.

Emmerova, M. & Jirava, F. (2004). Is Gulf War Syndrome really a mystery? *Med.Confl.Surviv., 20,* 209-217.
Since the end of the 1991 Gulf War about 20,000 United States veterans and similar proportions of troops from other allied contingents have been affected by a variety of symptoms which have collectively become known as 'Gulf War Syndrome'. Similar symptoms have been reported in Iraqi civilians including children. Despite extensive investigations no agreement has been reached on whether there is an underlying cause or causes. In this article, the principal features of the illness are summarised and some of the proposed causes discussed. It is proposed that the common cause is the toxic smoke from incomplete combustion of oil from burning wells, and this hypothesis is related to the known toxicology of two likely combustion products, nitric oxide and carbon monoxide. The effect of this proposal on possible investigations and treatment is considered.

Engel, C. C., Jaffer, A., Adkins, J., Riddle, J. R., & Gibson, R. (2004b). Can we prevent a second 'Gulf War syndrome'? Population-based healthcare for chronic idiopathic pain and fatigue after war. *Adv.Psychosom.Med., 25,* 102-122. (DoD)
In the 1991 Gulf War less than 150 of nearly 700,000 deployed US troops were killed in action. Today, however, over 1 in 7 US veterans of the war has sought federal healthcare for related-health concerns, and fully 17% of UK Gulf War veterans describe themselves as suffering from the 'Gulf War syndrome', a set of poorly defined and heterogeneous ailments consisting mainly of chronic pain, fatigue, depression and other symptoms. Even though over 250 million dollars of federally funded medical research has failed to identify a unique syndrome, the debate regarding potential causes continues and has included oil well smoke, contagious infections, exposure to chemical and biological warfare agents, and posttraumatic stress disorder. Historical analyses completed since the Gulf War have found that postwar syndromes consisting of chronic pain, fatigue, depression and other symptoms have occurred after every war in the 20th century. These syndromes have gone by a variety of names such as Da Costa's syndrome, irritable heart, shell shock, neurocirculatory asthenia, and battle fatigue. Though the direct causes of these syndromes are typically elusive, it is clear that war sets in motion an undeniable cycle of physical, emotional, and fiscal consequences for war veterans and for society. These findings lead to important healthcare questions. Is there a way to prevent or mitigate subsequent postwar symptoms and associated depression and disability? We argue that while idiopathic symptoms are certain to occur following any war, a population-based approach to postwar healthcare can mitigate the impact of postwar syndromes and foster societal, military, and veteran trust. This article delineates the model, describes its epidemiological foundations, and details examples of how it is being adopted and improved as part of the system of care for US military personnel, war veterans and families. A scientific test of the model's overall effectiveness is difficult, yet healthcare systems for combatants and their families are already being put to pragmatic tests as troops return from war in Iraq and Afghanistan and from other military challenges.

Ferguson, E., Cassaday, H. J., & Bibby, P. A. (2004a). Odors and sounds as triggers for medically unexplained symptoms: a fixed-occasion diary study of Gulf War veterans. *Ann.Behav.Med., 27,* 205-214.
BACKGROUND: Both laboratory studies on healthy volunteers and epidemiological evidence from patient samples indicate that odor can act as a trigger for the reporting of medically unexplained symptoms (MUSs). PURPOSE: The relationship between concurrent experiences of odor and MUSs has not been explored in a patient sample. METHODS: This study used an 8-day fixed-occasion diary study, in which 17 veterans of the Persian Gulf War completed diary assessments of (a) the intensity and duration of odor and sound and (b) MUS severity. RESULTS: The results showed that the intensity of odor was positively

associated with the severity on the same day and subsequent days' symptoms, whereas the duration of odor was negatively related to the severity of MUS reporting on the same day. CONCLUSIONS: These results are consistent with an associative mechanism underlying symptom reporting in veterans. By contrast, the duration, but not the intensity, of sound was related to the severity of MUS reporting on the same day.

Ferguson, E., Cassaday, H. J., Erskind, J., & Delahaye, G. (2004b). Individual differences in the temporal variability of medically unexplained symptom reporting. ***Br.J.Health Psychol., 9,*** **219-240.**
THEORY: Non-specific or medically unexplained symptoms account for up to 35% of outpatient referrals. In contrast to the literature on affect, little is known about how people frame daily symptoms and how these patterns are influenced by individual differences. METHOD: Three fixed occasion diary studies over an 8-day period (one on ill veterans of the Gulf War and two on healthy undergraduates) and a single cross-sectional survey (on ill Gulf War veterans) were conducted. The severity and frequency of daily symptoms were assessed in all daily diary samples, together with the Big 5 personality domains in one of the undergraduate samples and in the survey of veterans. The data were analysed using auto-correlations and hierarchical multivariate linear modeling. RESULTS: In all the chronically ill and healthy samples, the data suggested potential cyclical patterns for symptom severity reporting. With regard to the frequency of symptom reporting, the veterans showed a pattern of constant symptom reporting. Finally, the relationship between the reported severity of symptoms was attenuated by intellect and surgency. DISCUSSION: There is evidence that daily experiences of symptom severity are framed relative to each other and this relationship is influenced by personality. The practical implications of these findings are discussed.

Fiedler, N., Giardino, N., Natelson, B., Ottenweller, J. E., Weisel, C., Lioy, P. et al. (2004). Responses to controlled diesel vapor exposure among chemically sensitive Gulf War veterans. ***Psychosom.Med., 66,*** **588-598. (VA-005C, DoD-156)**
OBJECTIVE: A significant proportion of Gulf War veterans (GWVs) report chemical sensitivity, fatigue, and unexplained symptoms resulting in ongoing disability. GWVs frequently recall an association between diesel and petrochemical fume exposure and symptoms during service. The purpose of the present study among GWVs was to evaluate the immediate health effects of acute exposure to chemicals (diesel vapors with acetaldehyde) with and without stress. METHODS: In a single, controlled exposure to 5 parts per million (ppm) diesel vapors, symptoms, odor ratings, neurobehavioral performance, and psychophysiologic responses of 12 ill GWVs (GWV-I) were compared with 19 age- and gender-matched healthy GWVs (GWV-H). RESULTS: Relative to baseline and to GWV-H, GWV-I reported significantly increased symptoms such as disorientation and dizziness and displayed significantly reduced end-tidal CO_2 just after the onset of exposure. As exposure increased over time, GWV-I relative to GWV-H reported significantly increased symptoms of respiratory discomfort and general malaise. GWV-I were also physiologically hyporeactive in response to behavioral tasks administered during but not before exposure. CONCLUSIONS: Current symptoms among GWV-I may be exacerbated by ongoing environmental chemical exposures reminiscent of the Gulf War. Both psychologic and physiologic mechanisms contribute to current symptomatic responses of GWV-I.

Forbes, A. B., McKenzie, D. P., Mackinnon, A. J., Kelsall, H. L., McFarlane, A. C., Ikin, J. F. et al. (2004). The health of Australian veterans of the 1991 Gulf War: factor analysis of self-reported symptoms. ***Occup.Environ.Med., 61,*** **1014-1020. (Australian Department of Veterans' Affairs)**
BACKGROUND: A recent report showed that Australian veterans of the 1991 Gulf War displayed a greater prevalence of a multitude of self-reported symptoms than a randomly sampled comparison group of military personnel who were eligible for deployment but were not deployed to the Gulf. AIMS: To investigate whether the pattern, rather than frequency, of symptom reporting in these Australian Gulf War veterans differed from that of the comparison group personnel. METHODS: Factor analysis was used to determine whether the co-occurrence of 62 symptoms in 1322 male Gulf War veterans can be explained by a number of underlying dimensions, called factors. The methodology was also applied to 1459 male comparison group subjects and the factor solutions of the two groups were compared. RESULTS: For the Gulf War veterans, a three factor solution displayed replicability and construct validity. The three factors were labelled as psycho-physiological distress, somatic distress, and arthro-neuromuscular distress, and were broadly similar to those described in previous studies of Gulf War veterans. A concordant three factor solution was also found for the comparison group subjects, with strong convergence of the factor loadings and factor scores across the two groups being displayed. CONCLUSION: Results did not display evidence of a unique pattern of self-reported symptoms among Gulf War veterans. Results also indicated that the

differences between the groups lie in the degrees of expression of the three underlying factors, consistent with the well documented evidence of increased self-reported symptom prevalence in Gulf War veterans.

Gray, G. C., Gackstetter, G. D., Kang, H. K., Graham, J. T., & Scott, K. C. (2004). After more than 10 years of Gulf War veteran medical evaluations, what have we learned? *Am.J.Prev.Med., 26,* 443-452. (DoD-096)

Since the 1991 Gulf War, more than 10 years and 1 billion dollars of health evaluations and research have been invested in understanding illnesses among Gulf War veterans. We examined the extensive published healthcare utilization data in an effort to summarize what has been learned. Using multiple search techniques, data as of June 2003 from four different national Gulf War health registries and numerous hospitalization and ambulatory care reports were reviewed. Thus far, published reports have not revealed a unique Gulf War syndrome nor identified specific exposures that might explain postwar morbidity. Instead, they have demonstrated that Gulf War veterans have had an increase in multi-symptom condition, injury, and mental health diagnoses. While these diagnoses are similar to those experienced by other comparable military populations, their explanation is not fully understood. New strategies to identify risk factors for, and to reduce, such post-deployment conditions are summarized.

Haley, R. W., Vongpatanasin, W., Wolfe, G. I., Bryan, W. W., Armitage, R., Hoffmann, R. F. et al. (2004). Blunted circadian variation in autonomic regulation of sinus node function in veterans with Gulf War syndrome. *Am.J.Med., 117,* 469-478. (DoD-065, US Public Health Service, and Perot Foundation)

PURPOSE: To test the hypothesis that subtle abnormalities of the autonomic nervous system underlie the chronic symptoms reported by many Gulf War veterans, such as chronic diarrhea, dizziness, fatigue, and sexual dysfunction. METHODS: Twenty-two ill Gulf War veterans and 19 age-, sex-, and education-matched control veterans underwent measurement of circadian rhythm of heart rate variability by 24-hour electrocardiography, ambulatory blood pressure recording, Valsalva ratio testing, sympathetic skin response evaluation, sweat imprint testing, and polysomnography. Investigators were blinded to case- or control-group status. RESULTS: High-frequency spectral power of heart rate variability increased normally 2.2-fold during sleep in controls but only 1.2-fold in ill veterans ($P < 0.0001$). In ill veterans as compared with controls, it was lower at night ($P = 0.0006$), higher during the morning ($P = 0.007$), but no different during the rest of the day ($P = 0.8$). The mean heart rate of ill veterans also declined less at night ($P = 0.0002$), and their corrected QT intervals tended to be longer over the full 24 hours ($P = 0.07$), particularly at night ($P = 0.03$). Blunting of the nocturnal heart rate dip in ill veterans was confirmed by 24-hour automatic ambulatory blood pressure monitoring ($P = 0.05$) and polysomnography ($P = 0.03$). These differences remained significant after adjusting for potential confounders. Cases and controls were similar on measures of sympathetic adrenergic and sudomotor function, sleep architecture, respiratory function, and circadian variation in blood pressure and body temperature. CONCLUSION: Some symptoms of Gulf War syndrome may be due to subtle autonomic nervous system dysfunction.

Hotopf, M., David, A., Hull, L., Nikalaou, V., Unwin, C., & Wessely, S. (2004). Risk factors for continued illness among Gulf War veterans: a cohort study. *Psychol.Med., 34,* 747-754. (DoD-039 and UK Medical Research Council)

BACKGROUND: There are no prospective cohort studies of prognostic factors on the outcome of Gulf War veterans. We aimed to test the hypotheses that Gulf War veterans who were older; had more severe symptoms; had more exposures during deployment; had increased psychological distress and believed they had 'Gulf War syndrome' would experience greater fatigue and poorer physical functioning at follow-up. METHOD: Gulf War veterans who responded to an earlier retrospective cohort study were followed with a postal survey. More symptomatic individuals were oversampled. Outcome was measured on the Chalder fatigue questionnaire, the General Health Questionnaire and the Medical Outcome Study Short-Form 36. RESULTS: Of those surveyed, 73.8% responded. We found some evidence for four of the five hypotheses. More self-reported exposures at baseline were not associated with poorer outcome, but older people, those with more severe symptoms at baseline, those with psychological distress and who believed they were suffering from 'Gulf War syndrome' had more fatigue at follow-up. Officer status was associated with a better outcome. A similar lack of association was found for exposures and physical functioning and GHQ-12 score. 'Gulf War syndrome' attribution was associated with a worse outcome for GHQ-12 and physical functioning even after controlling for severity of symptoms at baseline. CONCLUSIONS: This study suggests that while multiple vaccination and military exposures are important risk factors for the onset of

symptoms in Gulf War veterans, these are not important risk factors for persistence of such symptoms. Instead the severity of the initial symptoms; psychological distress and attributions may be more important determinants of outcome.

Hunt, S. C., Richardson, R. D., Engel, C. C., Jr., Atkins, D. C., & McFall, M. (2004). Gulf War veterans' illnesses: a pilot study of the relationship of illness beliefs to symptom severity and functional health status. *J.Occup.Environ.Med., 46,* 818-827. (VA-058)
This investigation describes the illness beliefs of veterans regarding their Gulf War-related health concerns and investigates the relationship of these illness beliefs to physical and mental health functioning. Gulf War veterans (N = 583) presenting for evaluation at a Veteran's Affairs and Department of Defense facility completed self-report measures of symptom-related beliefs, psychosocial distress, and functional status. Hierarchical multiple regression analyses were performed to determine the extent that symptom-related beliefs impacted symptom-reporting and functional status independent of demographic factors and psychiatric illness. Several beliefs predicted physical symptom reporting and functional impairment in physical health and mental health domains after controlling for demographic variables and psychiatric illness. Gulf War veterans' illness beliefs may impact clinical outcomes. Discussing illness beliefs and providing accurate information is an important component of medical care for Gulf War veterans.

Hunter, D., Zoutman, D., Whitehead, J., Hutchings, J., & MacDonald, K. (2004). Health effects of anthrax vaccination in the Canadian forces. *Mil.Med., 169,* 833-838. (Canadian Department of National Defense)
OBJECTIVE: The objective of this study was to determine whether anthrax vaccine resulted in adverse health effects in Canadian Forces members 8 months after vaccination. METHODS: A quasi-experimental, retrospective chart review was undertaken for two groups within the Canadian Forces, one group that received anthrax vaccination and another that did not. Information on symptoms, diagnoses, and injuries for 848 persons for which there were approximately 35,000 chart entries was abstracted from charts over a 4.5-year period and was coded using the International Statistical Classification of Diseases and Related Health Problems, 10th edition. RESULTS: The chart retrieval rate was 84%. The mean number of chart entries per person was higher in the comparison group (43.4) than in the vaccine group (38.2). No statistically significant differences were seen in the percent change before and after vaccination in the number of chart entries for specific diagnoses and symptoms for the vaccine group compared with the comparison group. Visual inspection of the time trend in rates showed no unexplained increases in the rate of diagnosis and symptoms in the vaccine group after vaccination. CONCLUSION: This study found no evidence that the anthrax vaccination resulted in an increase in adverse health effects in the 8-month period after vaccination.

Karlinsky, J. B., Blanchard, M., Alpern, R., Eisen, S. A., Kang, H., Murphy, F. M. et al. (2004). Late prevalence of respiratory symptoms and pulmonary function abnormalities in Gulf War I Veterans. *Arch.Intern.Med., 164,* 2488-2491. (VA-002A)
BACKGROUND: Published reports have documented an increased prevalence of self-reported respiratory symptoms among servicemen deployed during the 1990-1991 Gulf War. We evaluated whether this deployment resulted in long-term adverse respiratory effects. METHODS: A comprehensive medical history was taken and physical and laboratory evaluations, including pulmonary function tests, were performed in 1036 deployed and 1103 non-deployed veterans of the Gulf War. Participants were classified into 5 groups on the basis of their pulmonary function tests findings: normal pulmonary function; nonreversible airway obstruction; reversible airway obstruction; restrictive lung physiology; and small airway obstruction. RESULTS: Deployed veterans were younger, more commonly white, less educated, single, of lower mean family incomes, and more likely to have enlisted than non-deployed veterans. Deployed veterans were also statistically more likely to self-report a history of smoking and wheezing than non-deployed veterans, but comparisons of reported physician visits for pulmonary complaints, pulmonary hospitalizations, numbers of documented episodes of asthma, bronchitis, or emphysema, and pulmonary medications prescribed in the year prior to evaluation did not reveal any differences between deployed and non-deployed veterans. The distribution of pulmonary function test results was identical among deployed and non-deployed veterans. Among both deployed and non-deployed veterans, about 64% had normal pulmonary function, 16% to 18% had nonreversible airway obstruction, 10% to 12.2% had restrictive lung physiology, 6% to 6.7% had small airway obstruction, and the remaining 0.9% to 1.3% had reversible airway obstruction. CONCLUSION: Our findings did not confirm the hypothesis that deployment to the Gulf War in 1990-1991 resulted in an increased prevalence of clinically significant pulmonary abnormalities 10 years later.

Kelsall, H. L., Sim, M. R., Forbes, A. B., McKenzie, D. P., Glass, D. C., Ikin, J. F. et al. (2004). Respiratory health status of Australian veterans of the 1991 Gulf War and the effects of exposure to oil fire smoke and dust storms. *Thorax, 59,* 897-903. (Australian Department of Veterans' Affairs)
BACKGROUND: Since the 1991 Gulf War concerns have been raised about the effects on veterans' health of exposures to Kuwaiti oil fire smoke and to dust storms. METHODS: A cross sectional study compared 1456 Australian Gulf War veterans with a randomly sampled military comparison group (n = 1588). A postal questionnaire asked about respiratory conditions, exposures, medications, tobacco use, demographic characteristics, and military service details. During a medical assessment, spirometric tests and a physical examination were performed and a respiratory questionnaire was administered. RESULTS: The response rate for the Gulf War veteran group was 80.5% and for the comparison group 56.8%. Australian Gulf War veterans had a higher than expected prevalence of respiratory symptoms and respiratory conditions suggesting asthma (OR 1.4; 95% CI 1.1 to 1.9) and bronchitis first diagnosed since the Gulf War (OR 1.9; 95% CI 1.2 to 3.1) but did not have poorer lung function or more ventilatory abnormalities than the comparison group. Veterans who reported exposure to oil fire smoke had slightly poorer forced vital capacity (difference between means -0.10 l; 95% CI -0.18 to -0.03) and those exposed to dust storms had a slightly better peak expiratory flow rate (difference between means 12.0 l/min; 95% CI 0.6 to 23.4) than veterans who did not report exposure. Veterans who were in the Gulf at or after the start of the oil fires had more respiratory conditions suggesting asthma (OR 1.7; 95% CI 1.0 to 2.9) than those who completed their deployment before this time. CONCLUSIONS: Increased self-reporting of respiratory symptoms, asthma, and bronchitis by veterans was not reflected in poorer lung function. The findings do not suggest major long term sequelae of exposure to oil fire smoke or dust storms.

Kelsall, H. L., Sim, M. R., Forbes, A. B., Glass, D. C., McKenzie, D. P., Ikin, J. F. et al. (2004). Symptoms and medical conditions in Australian veterans of the 1991 Gulf War: relation to immunisations and other Gulf War exposures. *Occup.Environ.Med., 61,* 1006-1013. (Australian Department of Veterans' Affairs)
AIMS: To investigate whether Australian Gulf War veterans have a higher than expected prevalence of recent symptoms and medical conditions that were first diagnosed in the period following the 1991 Gulf War; and if so, whether these effects were associated with exposures and experiences that occurred in the Gulf War. METHODS: Cross-sectional study of 1456 Australian Gulf War veterans and a comparison group who were in operational units at the time of the Gulf War, but were not deployed to that conflict (n = 1588). A postal questionnaire was administered and the likelihood of the diagnosis of self-reported medical conditions was assessed and rated by a medical practitioner. RESULTS: Gulf War veterans had a higher prevalence of all self-reported health symptoms than the comparison group, and more of the Gulf War veterans had severe symptoms. Increased symptom reporting was associated with several exposures, including having more than 10 immunisations, pyridostigmine bromide tablets, anti-biological warfare tablets, pesticides, insect repellents, reportedly being in a chemical weapons area, and stressful military service experiences in a strong dose-response relation. Gulf War veterans reported psychological (particularly post-traumatic stress disorder), skin, eye, and sinus conditions first diagnosed in 1991 or later more commonly than the comparison group. Over 90% of medical conditions reported by both study groups were rated by a medical practitioner as having a high likelihood of diagnosis. CONCLUSION: More than 10 years after the 1991 Gulf War, Australian veterans self-report all symptoms and some medical conditions more commonly than the comparison group. Further analysis of the severity of symptoms and likelihood of the diagnosis of medical conditions suggested that these findings are not due to over-reporting or to participation bias.

Kennedy, G., Abbot, N. C., Spence, V., Underwood, C., & Belch, J. J. (2004). The specificity of the CDC-1994 criteria for chronic fatigue syndrome: comparison of health status in three groups of patients who fulfill the criteria. *Ann.Epidemiol., 14,* 95-100. (Myalgic Encephalomyelitis Research Group for Education and Support)
PURPOSE: The Centers for Disease Control and Prevention (CDC)-1994 definition of chronic fatigue syndrome (CFS) is very broad, and there have been suggestions that it lacks specificity. To test this, we have compared three groups of patients, all of whom fulfill the criteria but self-report different etiologies. METHODS: Patients with self-reported symptoms which developed sporadically (sCFS, n=48); after Gulf War service (GW, n=24); and following exposure to organophosphate insecticides (OP, n=25) underwent a clinical examination, completed the MOS SF-36 quality of life and Hospital Anxiety and Depression scales, and were assessed for major and minor criteria for CDC-1994 CFS. RESULTS: Significant differences in simple clinical measures and outcome measures were observed between groups. The GW

group had significantly more severe physical symptoms-fatigue, muscle and multi-joint pain-than OP or sCFS, and the sCFS group was significantly less impaired than the other two groups in terms of emotional and mental health. In all three groups, a majority of patients exhibited muscle weakness in the lower limbs, and significant numbers of patients had absent or abnormal reflexes. CONCLUSIONS: Differences in simple, easily performed clinical outcome measurements can be observed between groups of patients, all of whom fulfill the CDC-1994 criteria for CFS. It is likely that their response to treatment may also vary. The specificity of the CFS case definition should be improved to define more homogeneous groups of patients for the purposes of treatment and research.

Khan, F., Kennedy, G., Spence, V. A., Newton, D. J., & Belch, J. J. (2004). Peripheral cholinergic function in humans with chronic fatigue syndrome, Gulf War syndrome and with illness following organophosphate exposure. *Clin.Sci.(Lond), 106,* 183-189. (Myalgic Encephalomyelitis Research Group for Education and Support)
In the present study, we have investigated whether the peripheral cholinergic abnormalities that we have reported previously [Spence, Khan and Belch (2000) Am. J. Med. 108, 736-739] in patients with chronic fatigue syndrome (CFS) are also present in those with Gulf War syndrome (GWS) and agricultural workers exposed to organophosphate pesticides, where cholinesterase inhibition is specifically implicated. We also looked at whether these abnormalities might be due to a reduction in the activity of cholinesterase expressed on the vascular endothelium. We used laser Doppler imaging to measure the forearm skin blood flow responses to iontophoresis of acetylcholine and of methacholine (which is resistant to breakdown by cholinesterase) in patients with CFS, GWS and those with a history of ill health after definite organophosphate exposure, as well as in matched healthy controls. The response to acetylcholine was significantly higher in patients with CFS than in controls (P =0.029, repeated-measures ANOVA), but was normal in those with GWS and those exposed to organophosphates. The methacholine response was higher than the acetylcholine response in all patient groups except for those with CFS, where there was no difference between the responses. Although there are many clinical similarities between these three illnesses, our results indicate peripheral cholinergic abnormalities in the vascular endothelium of only patients with CFS, suggesting that this syndrome has a different aetiology, which might involve inhibition of vascular cholinesterase.

Mahan, C. M., Kang, H. K., Dalager, N. A., & Heller, J. M. (2004). Anthrax vaccination and self-reported symptoms, functional status, and medical conditions in the National Health Survey of Gulf War Era Veterans and Their Families. *Ann.Epidemiol., 14,* 81-88. (VA-002A and VA-002B)
PURPOSE: To evaluate the health status of Gulf War veterans who reported receipt of anthrax vaccination and a small group of Gulf War veterans for whom documentation of anthrax vaccination exists. METHODS: Among the 11,441 Gulf War veterans who completed a health survey, 4601 reported receiving the anthrax vaccine during the war; 2979 veterans reported not receiving it; 3861 were uncertain. Also, 352 of these respondents were documented by the Department of Defense as having received anthrax vaccination. We compared the medical history of these groups of veterans using multivariate analyses. Finally, we analyzed perception of exposure and its relation to reporting bias. RESULTS: There were statistically significant differences in prevalence for almost all outcomes studied between those who reported having received anthrax vaccination and those who did not so report. However, when we compared the veterans for whom vaccination records exist to the group who self-reported that they had not received the vaccine, the significant differences in prevalence for almost all of the outcomes disappeared. CONCLUSIONS: The extent of a reporting bias should be carefully considered when one evaluates the health consequences of anthrax vaccination based on self-reported data.

McKeown-Eyssen, G., Baines, C., Cole, D. E., Riley, N., Tyndale, R. F., Marshall, L. et al. (2004). Case-control study of genotypes in multiple chemical sensitivity: CYP2D6, NAT1, NAT2, PON1, PON2 and MTHFR. *Int.J.Epidemiol., 33,* 971-978.
BACKGROUND: Impaired metabolism of toxic chemicals is a postulated mechanism underlying multiple chemical sensitivity (MCS). Because genetic variation alters the rate of chemical metabolism, this study was designed to determine if MCS cases differed from controls for genetic polymorphisms in drug-metabolizing enzymes. METHODS: Female Caucasian participants (203 cases and 162 controls) were drawn from a larger case-control study based on a reproducible and validated case definition. Common polymorphisms for CYP2D6, NAT1, NAT2, PON1, and PON2 were genotyped. RESULTS: Comparing cases and controls, significant differences were found in genotype distributions for CYP2D6 (P = 0.02) and NAT2 (P = 0.03). Compared with the referent homozygous inactive (CYP2D6) or slow (NAT2)

metabolizers, the odds for being CYP2D6 homozygous active (OR = 3.36, P = 0.01) and NAT2 rapid (OR = 4.14, P = 0.01) were significantly higher in cases than controls. The odds for being heterozygous for PON1-55 (OR = 2.05, P = 0.04) and PON1-192 (OR = 1.57, P = 0.04) were also significantly higher in cases. CONCLUSIONS: A genetic predisposition for MCS may involve altered biotransformation of environmental chemicals. The CYP2D6 enzyme activates and inactivates toxins; the NAT2 enzyme bioactivates arylamines to protein-binding metabolites. A gene-gene interaction between CYP2D6 and NAT2 suggested that rapid metabolism for both enzymes may confer substantially elevated risk (OR = 18.7, P = 0.002). Our finding parallels others' observation of a link between PON1 heterozygosity and neurological symptoms in Gulf War syndrome. This first demonstration of genetic variation in drug-metabolizing enzymes in association with MCS requires replication. However, it suggests new research directions on genetically variable toxin pathways that might be important in MCS.

Natelson, B. H. (2004). Stress, hormones and disease. ***Physiol Behav., 82,*** **139-143. (VA-005A)**
My postdoctoral training under Dr. Gerard Smith began me on a lifetime of investigation on the role of stress, hormones, and disease. The first set of experiments asked what hormone, if any, best reflected the range of aroused behaviors. We found that catecholamines performed substantially better than glucocorticoids did, despite the belief that glucocorticoids were sensitive indices of stress. But we also learned that hormones themselves were nowhere near as good in monitoring stress as motor behaviors were. In a second set of experiments, we tried to understand how stress affected medical disease. We learned that stress can produce disease in a healthy organism but has its most profound effects when disease already exists. Finally, in the early 1990s, I shifted my focus on stress and disease to a broader problem in behavioral medicine, namely, medically unexplained fatigue and pain. Among the studies we have done investigating these disorders, we looked specifically at veterans of the first Gulf War-many of whom developed problems with severe fatigue. A critical question in the literature asked if unexplained fatigue was simply a physical component of concurrent posttraumatic stress disorder (PTSD). In a large epidemiological study, we found that PTSD tracked stressor intensity in a stepwise fashion, while fatiguing illness increased with stressor intensity only on the milder side of the intensity spectrum. This result indicated that the two ailments are both stress sensitive but dissimilar.

Nisenbaum, R., Ismail, K., Wessely, S., Unwin, C., Hull, L., & Reeves, W. C. (2004). Dichotomous factor analysis of symptoms reported by UK and US veterans of the 1991 Gulf War. ***Popul.Health Metr., 2,*** **8. (DoD-039 and HHS-002**
BACKGROUND: Factor analysis is one of the most used statistical techniques to analyze the inter-relationships among symptoms reported by Gulf War veterans. The objective of this study was to apply factor analyses to binary symptom data from the UK study of Gulf War illness and the US Air Force study of Gulf War veterans, and to compare the symptom domains derived from the distinct samples. METHODS: UK veterans of the 1991 Gulf War (n = 3,454), individuals deployed to Bosnia on U.N. peacekeeping operations (n = 1,979) and Gulf War-era servicemen (n = 2,577) who were not deployed to the Gulf were surveyed in 1997-1998, and US 1991 Gulf War veterans from four Air Force units (n = 1,163) were surveyed in 1995 to collect health characteristics including symptoms. Each sample was randomly split in half for exploratory and confirmatory dichotomous factor analyses with promax oblique rotation. RESULTS: Four correlated factors were identified in each of the samples. Three factors (Respiratory, Mood-Cognition, and Peripheral Nervous) overlapped considerably across the UK cohorts. The Gastrointestinal/Urogenital factor in the UK Gulf cohort was noticeably different from the Gastrointestinal factor identified from the Bosnia and Era cohorts. Symptoms from Gulf War UK and U.S. cohorts yielded similar Gastrointestinal, Respiratory and Mood-Cognition factors, despite differences in symptom inventories between the two surveys. A Musculoskeletal factor was only elicited from the US Gulf sample. CONCLUSION: Findings of this report are consistent with those from other factor analysis studies that identified similar symptom dimensions between Gulf and non-Gulf War veterans, except that the Gastrointestinal factor in Gulf veterans included other symptom types. Correlations among factors raise the question as to whether there is a general illness, even if not unique to Gulf veterans, representing the common pathway underlying the identified factors. Hierarchical factor analysis models may be useful to address this issue.

Richardson, R. D. & Engel, C. C., Jr. (2004). Evaluation and management of medically unexplained physical symptoms. *Neurologist., 10,* 18-30. (VA-058)
BACKGROUND: Medically unexplained physical symptoms (MUPS) and related syndromes are common in medical care and the general population, are associated with extensive morbidity, and have a large impact on functioning. Much of medical practice emphasizes specific pharmacological and surgical intervention for discrete disease states. Medical science, with its emphasis on identifying etiologically meaningful diseases comprised of homogeneous groups of patients, has split MUPS into a number of diagnostic entities or syndromes, each with its own hypothesized pathogenesis. However, research suggests these syndromes may be more similar than different, sharing extensive phenomenological overlap and similar risk factors, treatments, associated morbidities, and prognoses. Examples of syndromes consisting of MUPS include chronic fatigue syndrome, fibromyalgia, multiple chemical sensitivities, somatoform disorders, and 'Gulf War Syndrome.' REVIEW SUMMARY: This paper is a narrative review of the increasing body of evidence suggesting that MUPS and related syndromes are common, disabling, and costly. It emphasizes that MUPS occur along a continuum of symptom count, severity, and duration and may be divided into acute, subacute (or recurrent), and chronic types. Predisposing, precipitating, and perpetuating factors influence the natural history of MUPS. CONCLUSIONS: Effective symptom management involves collaborative doctor-patient approaches for identification of problems based on a combination of medical importance and patient readiness to initiate behavioral change, negotiated treatment goals and outcomes, gradual physical activation and exercise prescription. Additionally, efforts should be made to teach and support active rather than passive coping with the symptoms.

Rose, M. R., Sharief, M. K., Priddin, J., Nikolaou, V., Hull, L., Unwin, C. et al. (2004). Evaluation of neuromuscular symptoms in UK Gulf War veterans: a controlled study. *Neurology, 63,* 1681-1687. (UK Ministry of Defense)
OBJECTIVES: To determine whether Gulf War veterans with neuromuscular symptoms that included weakness and fatigue had either 1) objective correlates for muscle weakness or fatigue; or 2) any etiologic explanation for such symptoms; and if so, 3) whether such objective measures or etiologic mechanisms were specific to Gulf War service. METHODS: Forty-nine ill Gulf War veterans with more than four neuromuscular symptoms (Gulf-ill) were compared with 26 Gulf-well veterans, 13 symptomatic Bosnian veterans (Bosnia-ill), and 22 symptomatic troops who were not deployed to the Gulf (Era-ill). Quantitative myometry was used to objectively measure weakness and fatigue. Subjects had an ischemic forearm exercise test, a subanaerobic bicycle exercise test, and a muscle biopsy. RESULTS: Quantitative strength and fatigue measures did not correlate with self-perception of weakness or fatigue for any of our groups. No specific muscle biopsy abnormalities were found. There was no defect of adenylate deaminase or glycogenolysis found. Gulf-ill subjects did find the subanaerobic bicycle exercise more effortful and generated significantly higher plasma lactate concentrations compared with health Gulf War subjects. CONCLUSION: Because complaints of weakness and fatigue in ill servicemen do not correlate with actual weakness or fatigue, explanations for these symptoms must lie outside of the neuromuscular system. Increased lactate production during subanaerobic bicycle exercise reflects mitochondrial inefficiency, but it is unclear whether this reflects mitochondrial damage sustained during Gulf War service or inactivity secondary to ill health.

Sadler, A. G., Booth, B. M., Mengeling, M. A., & Doebbeling, B. N. (2004). Life span and repeated violence against women during military service: effects on health status and outpatient utilization. *J.Womens Health (Larchmt.), 13,* 799-811. (DoD)
PURPOSE: To determine whether the type or frequency of intentional violence experiences among women during military service influences health status or healthcare utilization. Differences in utilization and health status were also examined while controlling for life span violence exposures and important patient characteristic confounders. METHODS: A cross-sectional survey of women veterans was conducted using a random sample stratified by region and era of service. Female veterans who served in the Vietnam and subsequent eras (n = 520) were selected from comprehensive women's healthcare centers' registries at Department of Veterans Medical Centers in Boston, Durham, Tampa, Minneapolis, Chicago, and Los Angeles (n = 8693). Socioeconomic information, violence exposure history, outpatient healthcare utilization, and assessment of health status (measured by the Medical Outcomes Study Short-Form 36) were obtained by structured telephone interview. RESULTS: The type of violence women experienced was unrelated to differences in medical utilization. Women reporting repeated violence exposures during military service had significantly more outpatient visits in the year preceding the interview than singly or non-traumatized peers (16 vs. 9 and 8 visits, respectively, $p < 0.05$). Repeatedly assaulted women also had

poorer health status ($p < 0.05$), and more often reported a history of childhood violence ($p < 0.001$) and postmilitary violence ($p < 0.001$). CONCLUSIONS: Repeated violence exposure is a relatively common experience among women in the military, and this has substantial implications for their health.

Schneiderman, A. I., Lincoln, A. E., Curbow, B., & Kang, H. K. (2004). Variations in health communication needs among combat veterans. *Am.J.Public Health, 94,* 2074-2076. (VA)
In this cross-sectional study of US military combat veterans, we assessed the helpfulness of different media for providing health risk communication messages. We have provided preliminary results from a postal survey of 5000 veterans sampled because of their deployment to Vietnam, the Persian Gulf, or Bosnia-Kosovo. Respondents endorsed the primary care provider as the most helpful source of health information. Access to the Internet and use of this medium for seeking health information differed by race, age, and cohort.

Schumm, W. R., Webb, F. J., Bollman, S. R., Jurich, A. P., Reppert, E. J., Castelo, C. S. et al. (2004). Predicting self-reported exposure to nerve agents by reserve component personnel during the first Persian Gulf War. *Psychol.Rep., 94,* 989-992.
Approximately 13% of 654 Reserve Component Gulf War veterans (18% women, 65% ground forces, between 24 and 61 years of age, average 40.2 yr.) surveyed in the Ohio Desert Storm Research Project reported that they had probably been exposed to nerve or mustard gas agents, while another 32% thought such exposures were possible. Reports of exposure were found, through ordinary least squares regression analysis, to be associated with membership in ground forces (Army/Marine Corps) ($b = .29$), geographical location ($b = .17$), ethnic minority status ($b = .07$), education ($b = -.10$), intrinsic religiosity ($b = .10$), and also reporting having had physiological reactions to vaccines or pyridostigmine bromide pills ($b = .24$). Reports were not associated significantly with subjective health before the war, age, or sex.

Sever, J. L., Brenner, A. I., Gale, A. D., Lyle, J. M., Moulton, L. H., Ward, B. J. et al. (2004). Safety of anthrax vaccine: an expanded review and evaluation of adverse events reported to the Vaccine Adverse Event Reporting System (VAERS). *Pharmacoepidemiol.Drug Saf, 13,* 825-840. (DoD)
PURPOSE: To assess the safety of a licensed anthrax vaccine (AVA) given to more than 500,000 US military personnel, through review and medical evaluation of adverse events (AEs) reported to the Vaccine Adverse Event Reporting System (VAERS). METHODS: AEs were summarized by person, vaccine lot, type, frequency and impact. A Delphic approach was used to tentatively assess causality in an effort to detect serious AEs (SAEs) or other medically important AEs (OMIAEs) possibly attributable to AVA. RESULTS: The Anthrax Vaccine Expert Committee (AVEC) reviewed 1841 reports describing 3991 AEs (9.4 reports/10,000 doses of AVA) that were submitted to VAERS from 1Q1998 through 4Q2001. One hundred forty-seven reports described an SAE or OMIAE, of which 26 were tentatively rated as possible, probable or certain consequences of vaccination (injection-site reaction [12], 'anaphylactic-like reaction' [5] and eight other systemic AEs [1-2 each]). CONCLUSIONS: This review produced no evidence for an unusual rate of any SAE or OMIAE attributable to AVA. It supported an earlier impression that AVA may cause significant local inflammation and should be administered over the deltoid rather than the triceps to avoid direct or compression injury to the ulnar nerve. The subjects of VAERS reports tended to be older than all recipients of AVA. Females generally had and/or reported AEs more often than males, but transient articular reactions were surprisingly more common in males. Variations in the frequency or severity (as judged by hospitalization and/or loss of duty) of reported AEs did not suggest a significant problem with (1) a particular lot of AVA, (2) recurrent AEs after multiple doses or (3) vaccination of persons with a concomitant illness or those given other vaccines or medications.

Simmons, R., Maconochie, N., & Doyle, P. (2004). Self-reported ill health in male UK Gulf War veterans: a retrospective cohort study. *BMC.Public Health, 4,* 27.
BACKGROUND: Forces deployed to the first Gulf War report more ill health than veterans who did not serve there. Many studies of post-Gulf morbidity are based on relatively small sample sizes and selection bias is often a concern. In a setting where selection bias relating to the ill health of veterans may be reduced, we: i) examined self-reported adult ill health in a large sample of male UK Gulf War veterans (GWV) and a demographically similar non-deployed comparison group (NGWV); and ii) explored self-reported ill health among veterans who believed that they had Gulf War syndrome. METHODS: This study uses data from a retrospective cohort study of reproduction and child health in which a validated postal questionnaire was sent to all GWV and a comparison cohort of Armed Service personnel who were not deployed to the Gulf. The cohort for analysis comprises 42,818 males who responded to the questionnaire.

RESULTS: We confirmed that GWV report higher rates of general ill health. GWV were significantly more likely to have reported at least one new medical symptom or disease since 1990 than NGWV (61% versus 37%, OR 2.7, 95% CI 2.5-2.8). They were also more likely to report higher numbers of symptoms. The strongest associations were for mood swings (OR 20.9, 95%CI 16.2-27.0), memory loss/lack of concentration (OR 19.6, 95% CI 15.5-24.8), night sweats (OR 9.9, 95% CI 6.5-15.2), general fatigue (OR 9.6, 95% CI 8.3-11.1) and sexual dysfunction (OR 4.6, 95%CI 3.2-6.6). 6% of GWV believed they had Gulf War syndrome (GWS), and this was associated with the highest symptom reporting.
CONCLUSIONS: Increased levels of reported ill health among GWV were confirmed. This study was the first to use a questionnaire which did not focus specifically on the veterans' symptoms themselves. Nevertheless, the results are consistent with those of other studies of post-Gulf war illness and thus strengthen overall findings in this area of research. Further examination of the mechanisms underlying the reporting of ill health is required.

Smith, T. C., Jimenez, D. L., Smith, B., Gray, G. C., Hooper, T. I., Gackstetter, G. D. et al. (2004a). The postwar hospitalization experience of Gulf War veterans participating in U.S. health registries. ***J.Occup.Environ.Med., 46,*** **386-397. (DoD-094)**
In response to concerns that Gulf War veterans were experiencing increased morbidity resulting from wartime exposures in the Gulf War, the Department of Veterans Affairs and the Department of Defense (DoD) initiated clinical registries to provide systematic health evaluations for self-referred Gulf War veterans. The authors used Cox's proportional hazard modeling with data from all DoD hospitals to estimate the probability of hospitalization resulting from any cause, resulting from diagnosis in a major diagnostic category, and resulting from a specific diagnosis of interest. After adjusting for other risk factors, registry participants were 1.43 times more likely to have a postwar hospitalization than registry nonparticipants (95% confidence interval, 1.40-1.46). These findings support the hypothesis that registry participants were more likely to experience postwar morbidity than veterans who chose not to enroll in the health registries.

Smith, T. C., Corbeil, T. E., Ryan, M. A., Heller, J. M., & Gray, G. C. (2004b). In-theater hospitalizations of US and allied personnel during the 1991 Gulf War. ***Am.J.Epidemiol., 159,*** **1064-1076. (DoD-096)**
The postwar morbidity of Gulf War veterans has been closely examined. However, data have not been available to evaluate morbidity suffered during the 1991 Gulf War. In this report, the authors examine archived records of hospitalizations in US military facilities in the Kuwaiti theater of operations or those medically evacuated to facilities in Europe. Using multivariable logistic regression modeling, the authors determined that service personnel at greatest odds for "in-theater" hospitalization were enlisted, female, white, Reservist, Army, and health care workers. No increase in odds was observed for oil well fire smoke exposure or possible exposure to the nerve agent hazard areas. Although these data may be incomplete, they represent the best-known data reflecting in-theater hospitalizations during the Gulf War of 1991 and show remarkable similarities in risk factors to those for postwar hospitalization.

Stein, P. K., Domitrovich, P. P., Ambrose, K., Lyden, A., Fine, M., Gracely, R. H. et al. (2004). Sex effects on heart rate variability in fibromyalgia and Gulf War illness. ***Arthritis Rheum., 51,*** **700-708. (DoD-031 and National Institutes of Health)**
OBJECTIVE: To investigate autonomic abnormalities in male and female fibromyalgia (FM) and Gulf War illness (GWI) patients by comparing heart rate variability (HRV) with that of age- and sex-matched healthy controls. METHODS: Subjects included 26 (19 women, 7 men) with FM, 11 (6 men, 5 women) with GWI, and 36 (18 men, 18 women) healthy controls. HRV was determined from Holter recordings obtained in the Clinical Research Center. Analysis of variance compared 24-hour, daytime, and nighttime HRV by sex within groups and by group within sex. RESULTS: In women with FM or GWI, HRV was significantly lower than in men with FM or GWI. HRV was similar in male and female controls. When HRV was compared by group within sex, HRV was significantly decreased in women with FM or GWI and no significant differences were seen for men with these conditions. CONCLUSION: Decreased HRV in FM and GWI appears to be sex dependent. Results suggest that different mechanisms may be operative in symptom expression in men and women with this spectrum of illness.

Sulsky, S. I., Grabenstein, J. D., & Delbos, R. G. (2004). Disability among U.S. Army personnel vaccinated against anthrax. *J.Occup.Environ.Med., 46,* 1065-1075. (DoD)
This study was conducted to examine whether U.S. Army personnel receiving > or =1 dose of anthrax vaccine adsorbed (AVA) between March 1998 and February 2002 were at higher risk of disability than unvaccinated personnel. We studied a historical cohort study of 716,833 active-duty soldiers (154,456 vaccinated) followed for 4.25 years to determine rates of evaluation for disability discharge. Cox proportional hazards models compared estimated risk of evaluation for disability, accounting for occupation and sociodemographics. Adjusted hazard ratio (HR) and 95% confidence interval (CI) was 0.96 (CI = 0.92-0.99). Separate adjusted HRs for men, women, permanent and temporary disability, musculoskeletal and neurologic conditions were similar, ranging from 0.90 to 1.04. Latency assumptions did not affect results. Anthrax vaccination does not increase risk of disability. This finding may be partially the result of factors influencing selection for vaccination or vaccine tolerance.

Vladutiu, G. D. & Natelson, B. H. (2004). Association of medically unexplained fatigue with ACE insertion/deletion polymorphism in Gulf War veterans. *Muscle Nerve, 30,* 38-43.
Genes associated with muscle metabolism and physical endurance were evaluated for variants that may contribute to the etiology of medically unexplained severe and chronic fatigue. Subjects included 49 Gulf War veterans and 61 nonveterans with chronic fatigue syndrome (CFS) or idiopathic chronic fatigue (ICF) and 30 veterans and 45 nonveterans who served as healthy controls. Increased risk for CFS/ICF was associated with alterations of the insertion/deletion (I/D) polymorphism in the angiotensin-converting enzyme (ACE) gene within the Gulf War veteran sample only. The I allele frequency was decreased in affected versus unaffected veterans (0.15 versus 0.48; odds ratio [OR], 5.08; 95% confidence interval [CI], 1.97-13.35; P < 0.0001). Correspondingly, the II genotype was decreased fourfold in affected veterans (0.08 versus 0.35; OR = 5.87; 95% CI: 1.21-28.36; P = 0.02), and the DD genotype was increased twofold (0.78 versus 0.39; OR, 5.4; 95% CI, 1.6-18.4; P = 0.007). Veterans with the DD genotype were eight times more likely to develop CFS/ICF than were those with the II genotype (OR, 8.30; 95% CI, 1.50-56.09; P = 0.009).

Zavestoski, S., Brown, P., McCormick, S., Mayer, B., D'Ottavi, M., & Lucove, J. C. (2004). Patient activism and the struggle for diagnosis: Gulf War illnesses and other medically unexplained physical symptoms in the US. *Soc.Sci.Med., 58,* 161-175.
We examine Gulf War illnesses-which include the fatigue, joint pain, dermatitis, headaches, memory loss, blurred vision, diarrhea, and other symptoms reported by Gulf War veterans-in relation to other medically unexplained physical symptoms such as multiple chemical sensitivity, chronic fatigue syndrome, and fibromyalgia. Our intent is to examine the diagnosis negotiations involved in these mysterious diseases, by showing the different forms of legitimacy involved in such interactions. Factors involved in diagnostic legitimacy are: diagnostic legitimacy in the medical community, lay acceptance of the diagnosis, uncertainty in looking for causes, and social mobilization. We conclude by noting that research may not be able to find any cause for these diseases/conditions; hence, it may be necessary to embrace medical uncertainty, and also to accept patient experience in order to facilitate diagnosis, treatment, and recovery process. Such a change can alter patients' expectations and taken-for-granted assumptions about medicine, and perhaps in turn reduce the frequency with which dissatisfied individuals form illness groups that mobilize to challenge what they see as an unresponsive medical system.

III. RESEARCH FUNDING TRENDS

A. Overview

Appendix A provides information on the projects that VA, DoD, and HHS have funded. This appendix reflects data as of the end of FY 2004. Research projects are grouped according to the department that is responsible for their funding.

Appendix B is a categorized listing of all federally funded Gulf War research projects, regardless of the agency providing the funding. Three descriptors are used to categorize each funded project.

The first descriptor is the primary **Research Focus** of the project. The five Research Focus Areas, also used to organize the 21 Research Topics (see Section V), are:

- Brain and Nervous System Function (e.g., studies on central nervous system, autonomic nervous system, chronic pain, etc.)
- Environmental Toxicology (e.g., studies focused on specific environmental exposures such as pesticides, oil well fires, vaccines, medical prophylactic agents, etc.)
- Immune Function and Infectious Diseases
- Reproductive Health
- Symptoms and General Health (e.g., mortality, pulmonary disease, cancer, etc.)

Secondary and/or tertiary Research Focus Areas from the above list may also be assigned. Two additional Focus Areas may be used for secondary and tertiary assignments: This permits accounting for projects that cover multiple focus areas.

- Chemical weapons (e.g., sarin, sulfur mustard, etc.)
- Pyridostigmine bromide

The second descriptor is the **Project Focus**, categorized as follows:

- Diagnosis (i.e., studies that will improve the ability to diagnose previously unexplained conditions, or to better refine diagnoses with new tools)
- Exposure
- Interactions of exposures (chemical, biological, pharmacological, physiological, etc.)
- Prevention of diseases (i.e., studies that will produce knowledge that could lead to disease prevention strategies)
- Prevalence and risk factors for symptoms and alterations in general health status
- Treatment

Each project is assigned up to three Project 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 third descriptor for each project is **Research Type**. The Federal Government defines research as systematic investigation designed to develop or contribute to generalizable knowledge. Each research project on Gulf War veterans' illnesses uses a method of approach to test a specific research hypothesis. Approaches range in type from mechanistic research, addressing potential biological mechanisms of causation, to clinical and epidemiological research that attempt to determine illness prevalence and risk factors. Although precise categorization of research types can be difficult because of overlapping methodologies, research projects can be divided into the following general types:

MECHANISTIC RESEARCH: Research into underlying mechanisms of diseases and illnesses using in vitro and in vivo models.

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

EPIDEMIOLOGY RESEARCH: Study of the distribution and determinants of disease in human populations. It includes population-based studies focused on outcomes such as mortality, symptoms, hospitalizations, etc., using devices such as postal surveys, telephone interviews, and reviews of medical records.

In addition to the research on Gulf War veterans' illnesses, the Deployment Health Working Group (DHWG) also tracks development activities. In general, development is the systematic use of the knowledge or understanding gained from research directed toward the production of materials; devices; systems; or methods, including design, development, and improvement of prototypes and new processes. Within the context of Gulf War veterans' illnesses, the DHWG categorizes activities as development as follows:

DEVELOPMENT: An activity that satisfies the general definition of development described above, and is directed toward new biologically based prevention, intervention, and treatment measures.

The research database on Gulf War veterans' illnesses catalogs only research and development activities that either directly involve Gulf War veterans or have been initiated to answer specific questions about risk factors. An example of the latter is a research project using animal models to determine health effects of low-level chemical warfare agents. The database does not account for the vast accumulated knowledge derived from the nation's investment in biomedical research over the past 50 years.

The research database on Gulf War veterans' illnesses contains research that is Federally sponsored only. This includes research conducted by Federal scientists, as well as that by non-federal scientists supported by Federal research funds through grants, contracts, and cooperative agreements. It is not possible to accurately track research efforts that fall within the private sector or otherwise outside of the purview of the Federal government.

Nonetheless, the DHWG attempts to stay abreast of all research relevant to Gulf War veterans' illnesses. The DHWG accomplishes this by monitoring peer-reviewed published scientific literature, attending scientific meetings, and even using newspaper reports and personal accounts of researchers.

An interim assessment of the nature and causes of illnesses in Gulf War veterans was included in Appendix C of the Annual Report to Congress for 2000 (MVHCB, 2001) In 1996, the Persian Gulf Veterans Coordinating Board identified 21 major research questions. The comprehensive Gulf War research portfolio has addressed each of these questions, and relevant results have been published on each one.

The following sections provide a quantitative overview of the current research portfolio on Gulf War veterans' illnesses and the evolution of the portfolio over time since 1995. Topics that are covered include overall research expenditures from 1995-2004, and the types and areas of research in which the Federal Government has invested.

B. Research Funding Trends

From FY 1992 through FY 2004, VA, DoD, and HHS sponsored a total of 267 distinct research projects on Gulf War veterans' illnesses.

Appendix A lists all of the research and development projects and programs supported now or in the past by each of the three federal agencies (DoD, HHS, and VA). The appropriated funds for FY 1995 through 2004, centrally obligated to each project, are shown in Appendix C. Funds obligated for projects prior to 1995 are not shown in Table III-1 or Appendix C. Since many projects are multi-year efforts for which funds are obligated at the beginning of the project period, projects that received all of their funds prior to 1995 are listed with no associated obligation ($0) in Appendix C. Federal funds for these earlier projects were reported in prior Annual Reports to Congress.

Table III-1 is a summary of research expenditures by DoD, VA, and HHS for FY1995 through FY2004. Federal funding for Gulf War research totaled $260.2 million during this period. As of September 30, 2004, 192 projects were completed (71.9% of the 267 projects), and 75 projects (28.1%) were new or ongoing.

Table III-1. 10-Year (FY 1995-2004) Funding Trends for Gulf War Research in Millions of Dollars

Department	FY'95	FY'96	FY'97	FY'98	FY'99	FY'00	FY'01	FY'02	FY'03	FY'04	Total Costs FY'95-04
DoD	$11.0	$11.9	$28.9	$13.2	$22.7	$23.8	$28.8	$18.8	$12.4	$15.3	**$ 186.8**
HHS	$ 2.5	$ 1.6	$ 0.0	$ 1.6	$ 1.6	$ 1.6	$ 1.0	$ 0.8	$ 1.0	$ 0.5	**$ 12.2**
VA	$ 2.3	$ 3.9	$ 2.8	$ 4.7	$ 9.0	$12.0	$ 8.6	$ 4.5	$ 5.7	$ 7.7	**$ 61.2**
Total	**$15.8**	**$17.4**	**$31.7**	**$19.5**	**$33.3**	**$37.4**	**$38.4**	**$24.1**	**$19.1**	**$23.5**	**$ 260.2**

Table III-2 is a year-by-year accounting of new and completed projects.

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

Fiscal Year	New	Completed
1995	39	9
1996	20	3
1997	31	11
1998	17	16
1999	33	21
2000	21	44
2001	25	27
2002	12	46
2003	12	5
2004	14*	7

* Includes 7 ongoing projects identified in a 2005 VA Portfolio review

IV. NEW RESEARCH PROJECTS AND INITIATIVES

A. New Projects

This section highlights new research projects that have been approved for funding since last year's *Annual Report to Congress*. These projects all received funding in FY2004 and are included in Appendices A-C.

VA initiated funding for six new projects during FY2004 focused on Brain and Nervous System Function (3), Immune Function and Infectious Diseases (1), and Symptoms and General Health (2).

VA-091, "The Role of Dietary Choline in Neuroprotection," will test the hypothesis that dietary choline is neuroprotective in a rat model of neurotoxicity: N-methyl-D-aspartate (NMDA) antagonist-induced neurotoxicity in the cingulated and retrosplenial cortices (C/RSC).

VA-094, "The Immunology of Chronic Cutaneous Leishmaniasis," will examine factors that regulate chronic Leshmania infection and provide essential new information about basic immunologic processes that limit Th1 (cell-mediated) immune responses with the hope of developing strategies to reverse these suppressive pathways.

VA-096, "Functional Imaging of Pain in Veterans with Unexplained Muscle Pain," will employ functional magnetic resonance imaging (fMRI) to examine pain processing in Gulf War veterans with medically unexplained musculoskeletal pain. The hypothesis is that Gulf War veterans with musculoskeletal pain complaints will report significantly lower heat pain thresholds, significantly higher heat pain ratings, and steeper psychophysical curve estimates, suggestive of altered central pain sensitivity. Gulf War veterans with musculoskeletal pain are expected to exhibit a significantly greater fMRI response to both non-painful and painful heat stimuli compared to healthy, pain-free veteran controls.

VA-098, "Post-Transcriptional Gene Regulation of VEGF in Malignant Gliomas," will test the hypothesis that RNA stabilization of VEGF in glioblastoma cells results from the modulation of ribonucleoprotein (RNP) complexes formed by cellular factors and the 3' untranslated region (3UTR) of VEGF mRNA. The broad, long-term goal of this work is to elucidate the molecular pathway of RNA stabilization in malignant tumors and ultimately its potential as a target for anti-cancer therapy.

VA-101, "Biomarkers Discovery in ALS," will (1) further characterize and sequence novel biomarkers of ALS clinical progression, (2) test the hypothesis that ALS among Gulf War Veterans represents a novel variant of the disease based on protein expression profile analysis, and 3) explore the predicative role of ALS biomarkers in the progression of ALS type spinal cord dysfunction in an animal model of ALS.

VA-104, "Characterization of Pain Processing Mechanisms in the Irritable Bowel Syndrome," will test the hypothesis that patients with irritable bowel syndrome (IBS), a gastrointestinal disorder characterized by chronic abdominal pain, diarrhea and/or constipation, have alterations in central pain processing mechanisms that may cause hypersensitivity. The objectives will be accomplished by systematically applying and comparing pharmacological and psychophysical tests to IBS patients and controls. These studies will lead to larger clinical trials with potential therapeutic agents for veterans with IBS.

Seven additional ongoing projects (VA-095, VA-097, VA-099, VA-100, VA-102, VA-103, and VA-105) were added to the VA Gulf War research portfolio as a result of a complete portfolio review in November 2005. The details of this portfolio review will be fully described in the 2005 Annual Report to Congress.

HHS initiated funding for one new project during FY2004 focused on Brain and Nervous System Function.

HHS-012, "Epidemiology of ALS in Veterans," will test the hypothesis that gene-environment interactions may play a substantial role in ALS pathogenesis. Environmental risk factor information will be collected from ALS patients from the VA National ALS Registry and controls, and combined with genotyping for single-nucleotide polymorphisms (SNPs) and mitochondrial haplogroups to identify genetic and non-genetic risk factors for ALS as well as gene-environment interactions. Genetic and environmental effects on disease progression will also be examined.

B. New Initiatives

Request for Applications on the Etiology, Pathogenesis, and Treatment of ALS (RFA-NS-04-003)

On August 8, 2003 a joint Request for Applications (RFA-NS-04-003) was issued by the Department of Veteran's Affairs (VA), National Institute of Neurological Disorders and Stroke (NINDS), and The Amyotrophic Lateral Sclerosis Association (ALSA) for research proposals that address the etiology, pathogenesis, and treatment of amyotrophic lateral sclerosis. Sixty-nine proposals were received by the submission deadline of October 22, 2003, and reviewed on January 22, 2004. Of the eight projects selected for funding, one (VA-101) was determined to be directly relevant to the illnesses affecting Gulf War veterans.

VA Request for Applications on Gulf War Veterans Research

In April 2004, the VA Office of Research and Development issued a Request for Applications (RFA) on Gulf War Veterans Research. Forty-five proposals were received by the application deadline of June 25, 2004. These proposals were reviewed on September 14-15, 2004. Since they did not receive funds until October 1, 2004 (the first quarter of FY 2005), proposals selected for funding from this RFA will be included in the Annual Report to Congress on Federally Sponsored Research on Gulf War Veterans' Illnesses for 2005.

C. Ongoing Initiatives

VA Program Announcement on Deployment Health Research

On October 18, 2002, the VA Office of Research and Development issued a Program Announcement on Deployment Health Research in recognition of the high priority for development of improved methods of diagnosis, treatment, and prevention of illnesses related to hazardous deployments, such as the Gulf War, Bosnia/Kosovo, Afghanistan, and the current war in Iraq. The Program Announcement recognized five major research priorities:

- Long-term health impacts of hazardous deployments
- Health impacts of specific military occupational and environmental exposures
- Improvements in evaluation and diagnosis of deployment-related illnesses
- Improvements in treatment of deployment related illnesses
- Health risk communication for veterans and health care providers

Funding of one new project (VA-091) in FY 2004 resulted from this Program Announcement. The complete Program Announcement can be accessed at the following URL:
www.va.gov/resdev/fr/ProgramAnnouncementDeploymentHealthIssues.pdf

V. RESEARCH PRIORITIES

VA, DoD, and HHS created the Persian Gulf Veterans Coordinating Board (PGVCB) to coordinate research on Gulf War veterans' illnesses. In 1995, the PGVCB decided to provide a contextual framework for the results of completed and ongoing studies and also to develop an approach for the interpretation of research results. To that end, the PGVCB identified 19 major research questions and subsequently added 2 additional questions in 1996 (PGVCB, 1996a). The comprehensive Gulf War research portfolio has addressed each of these 21 questions, and relevant results have been published on each one. The Medical and Veterans Health Coordinating Board (MVHCB), the successor organization to the PGVCB, conducted a comprehensive assessment of the progress made on each of these 21 questions in the *Annual Report to Congress for 2000* (MVHCB, 2001a).

A. Twenty-One Research Topics

The Research Subcommittee of the Deployment Health Working Group (DHWG), the successor organization to the MVHCB, recently evaluated these 21 questions to determine if they remained a valid conceptual framework. Two modifications to the 21 questions have been made in the preparation of this report. The first is to convert the 21 questions to 21 research topic areas. This change reflects the current funding of projects focused on pathophysiological mechanisms and treatment in addition to epidemiology studies. The second change is to group the 21 topics into 5 major Research Focus Areas; Brain and Nervous System Function, Environmental Toxicology, Immune Function and Infectious Diseases, Reproductive Health, and Symptoms and General Health Status. The new organization of the Federal Gulf War research portfolio is presented below (the original 21 Research Questions are presented on the following page):

Brain & Nervous System Function

- Organic neuropsychological and neurological deficits (Question 16)
- Psychological symptoms and/or diagnoses (Question 18)

Environmental Toxicology

- Petroleum products and combustion products (Question 3)
- Occupational/environmental hazards (Question 4)
- Organophosphorus nerve agent and/or sulfur mustard from bombing at Muhammadiyat (Question 5) or weapons bunker at Khamisiyah
- Chemical agents, other than at Khamisiyah (Question 6)
- Pyridostigmine bromide and other medical prophylaxes (e.g. vaccines) (Question 7)
- Psychophysiological stressors (Question 8)
- Short term, low level exposures to pyridostigmine bromide, DEET, or permethrin, alone or in combination, cause short-term and/or long-term neurological effects (Question 17)

Immune Function and Infectious Diseases

- Leishmania tropica (Question 2)
- Altered immune function or host defense (Question 10)
- Other infectious diseases (Question 19)

Reproductive Health

- Birth defects in offspring (Question 11)
- Lower reproductive success (Question 12)
- Sexual dysfunction (Question 13)

Symptoms and General Health Status

- Symptoms/illnesses (Question 1)
- Nonspecific symptoms and symptom complexes (Question 9)
- Pulmonary symptoms or diagnoses (Question 14)
- Smaller baseline lung function or greater degree of nonspecific airway reactivity (Question 15)
- Development of cancers of any type (Question 20)
- Mortality rates (Question 21)

B. Twenty-One Original Research Questions

1. What is the prevalence of symptoms/illnesses in the Persian Gulf veteran population? How does this prevalence compare to that in an appropriate control group?
2. What was the overall exposure of troops to Leishmania tropica?
3. What were the exposure concentrations to various petroleum products, and their combustion products, in typical usage during the Persian Gulf conflict?
4. What was the extent of exposure to specific occupational/environmental hazards known to be common in the Persian Gulf veterans' experience? Was this exposure different from that of an appropriate control group?
5. What were the potential exposures of troops to organophosphorus nerve agent and/or sulfur mustard as a result of allied bombing at Muhammadiyat and Al Muthanna, or the demolition of a weapons bunker at Khamisiyah?
6. What was the extent of exposure to chemical agent, other than at Khamisiyah, Iraq, in the Persian Gulf as a function of space and time?
7. What was the prevalence of pyridostigmine bromide use among Persian Gulf troops?
8. What was the prevalence of various psycho physiological stressors among Persian Gulf War veterans? Is the prevalence different from that of an appropriate control population?
9. Are Persian Gulf veterans more likely than an appropriate comparison group to experience non-specific symptoms and symptom complexes?
10. Do Persian Gulf veterans have a greater prevalence of altered immune function or host defense when compared with an appropriate control group?
11. Is there a greater prevalence of birth defects in the offspring of Persian Gulf veterans than in an appropriate control population?
12. Have Persian Gulf Veterans experienced lower reproductive success than an appropriate control population?
13. Is the prevalence of sexual dysfunction greater among Gulf veterans than among an appropriate comparison population?
14. Do Gulf War veterans report more pulmonary symptoms, or diagnoses, than persons in appropriate control groups?
15. Do Gulf War veterans have a smaller baseline lung function in comparison to an appropriate control group? Do Gulf War veterans have a greater degree of non-specific airway reactivity in comparison to an appropriate control group?
16. Is there a greater prevalence of organic neuropsychological and neurological deficits in Persian Gulf veterans compared to appropriate control populations?
17. Can short-term, low-level exposures to pyridostigmine bromide, the insect repellant DEET, and the insecticide permethrin, alone or in combination, cause short-term and/or long-term neurological effects?
18. Do Persian Gulf veterans have a significantly higher prevalence of psychological symptoms and/or diagnoses than do members of an appropriate control group?
19. What id the prevalence of Leishmaniasis and other infectious diseases in the Gulf War veteran population?
20. Do Gulf War veterans have a greater risk of developing cancers of any type when compared with an appropriate control population?
21. Are Gulf War veterans experiencing a higher mortality rate than that of an appropriate control population? Are specific causes of death related to service in the Persian Gulf region?

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Appendices

Federally Funded Research Projects

Appendix A

Project Index By Department

DEPARTMENT OF DEFENSE PROJECTS

DoD-001	Naval Health Study Program
DoD-001A	Epidemiologic Studies of Morbidity Among Gulf War Veterans: A Search for Etiologic Agents and Risk Factors; A Study of Symptoms Among 1500 Seabees
DoD-001B	Epidemiologic Studies of Morbidity Among Gulf War Veterans: A Search for Etiologic Agents and Risk Factors; Study 2: A Comparative Study of Hospitalizations among Active-Duty Personnel Who Participated in the Gulf War and Similar Personnel Who Did Not
DoD-001C	Epidemiologic Studies of Morbidity Among Gulf War Veterans: A Search for Etiologic Agents and Risk Factors; Study 3: A comparative study of pregnancy outcomes among Gulf War veterans and other active-duty personnel
DoD-001D	Epidemiologic Studies of Morbidity Among Gulf War Veterans: A Search for Etiologic Agents and Risk Factors; Study 4: Infertility and Miscarriage in Gulf War Veterans
DoD-001E	Epidemiologic Studies of Morbidity Among Gulf War Veterans: A Search for Etiologic Agents and Risk Factors; Study 5: Seabee Health Study
DoD-001F	Epidemiologic Studies of Morbidity Among Gulf War Veterans: A Search for Etiologic Agents and Risk Factors; Study 6: A Comparison of Nonfederal Hospitalization Experience Among Veterans in California who have separated from active service: GWV vs. NDV
DoD-001G	Epidemiologic Studies of Morbidity Among Gulf War Veterans: A Search for Etiologic Agents and Risk Factors; Study 7: Prevalence of Congenital Anomalies Among Children of Persian Gulf War Veterans
DoD-002	Physiological and Neurobehavioral Effects in Rodents from Exposure to Pyridostigmine, Fuels, and DEET
DoD-004	The General Well-Being of Gulf War Era Service Personnel from the States of Pennsylvania and Hawaii: A Survey
DoD-007A	Health Risk Assessment of Embedded Depleted Uranium: Behavior, Physiology, Histology, and Biokinetic Modeling
DoD-007B	Carcinogenicity of Depleted Uranium Fragments
DoD-008A	Serologic Diagnosis of Viscerotropic Leishmaniasis (VTL)
DoD-008B	Development of a Leishmania Skin Test Antigen (LSTA)
DoD-009	Identification of the Genetic Factors Which Control Tropism in Leishmania
DoD-010	Pyridostigmine Synergistic Toxicity Study
DoD-011	Male/Female Differential Tolerances to Pyridostigmine Bromide
DoD-013	Effects of Persian Gulf War Service on Military Working Dogs

DoD-014	Risk Factors Among US Army Soldiers for Enrolling on the Department of Veterans Affairs Gulf War Registry
DoD-015	Comparative Mortality Among US Military Personnel Worldwide During Operations Desert Shield and Desert Storm
DoD-016	Kuwait Oil Fire Health Risk Assessment
DoD-017	Retrospective Studies Involving Military Use of Pyridostigmine as a Pretreatment for Nerve Agent Poisoning
DoD-018	Kuwait Oil Fires Troop Exposure Assessment Model (TEAM)
DoD-019	Persian Gulf Veterans Health Tracking System
DoD-021	Study of Variability In Pyridostigmine Inhibition of Blood Cholinesterases in Healthy Adults and Individuals With Symptoms Following Participation in Operation Desert Storm
DoD-022	Chronic Organophosphorus Exposure and Cognition
DoD-023	Acute and Long-Term Impact of Deployment to Southwest Asia on the Physical and Mental Health of Soldiers and their Families
DoD-030	Epidemiological Studies Persian Gulf War Illnesses, PG Women's Health Linkage Study
DoD-031	Dysregulation of the Stress Response in the Persian Gulf Syndrome
DoD-032	Neuropsychological Functioning in Persian Gulf Era Veterans
DoD-033	Effects of Pyridostigmine in Flinders Line Rats Differing in Cholinergic Sensitivity
DoD-034	Characterization of Emissions from Heaters Burning Leaded Diesel Fuel in Unvented Tents
DoD-035	Feasibility of Investigating Whether There is a Relationship Between Birth Defects and Service in the Gulf War.
DoD-036	Fatigue in Persian Gulf Syndrome-Physiologic Mechanisms
DoD-037	Neurobehavioral and Immunological Toxicity of Pyridostigmine, Permethrin, and DEET in Male and Female Rats
DoD-038	Diagnostic Antigens of Leishmania tropica
DoD-039	A Controlled Epidemiological and Clinical Study into the Effect of Gulf War Service on Servicemen and Women of the United Kingdom Armed Forces
DoD-040	Psychological and Neurobiological Consequences of the Gulf War Experience
DoD-041	Evaluation of Muscle Function in Persian Gulf Veterans
DoD-042	The Symptomatic Persian Gulf Veterans Protocol: An Analysis of Risk Factors with an Immunologic and Neuropsychiatric Assessment

DoD-044	Investigation of Seminal Plasma Hypersensitivity Reactions
DoD-045	Air Force Women's Health Surveillance Study
DoD-046	Exploratory Data Analysis with the CCEP Database
DoD-047	Study of Mycoplasmal Infections in Gulf War Veterans
DoD-048	Assessment of Genomic Instability via Chromosome 7 Inversion Frequency in a Gulf-War Syndrome Cohort vs Selected Control Groups
DoD-049	Diagnosis and Dosimetry of Exposure to Sulfur Mustard: Development of Standard Operating Procedures and Exploratory Research on Protein Adducts
DoD-050	Toxicokinetics of 0-Ethyl S-(2-Diisopropylaminoethyl) Methylphosphonothioate [(+)-VX] in Rats, Hairless Guinea Pigs and Marmosets - Identification of Metabolic Pathways
DoD-051	Transgenic Engineering of Cholinesterases: Tools for Exploring Cholinergic Responses
DoD-052	Female Gender and Other Potential Predictors of Functional Health Status Among Persian Gulf War Veterans
DoD-053	Long-Term Effects of Subclinical Exposures to Sarin
DoD-054	Assessment of Subchronic Neurobehavioral and Neuropathologic Effects in Rats Following Low-Level Sarin Exposure
DoD-055	Low-Level Exposure to GB Vapor in Air: Diagnosis/Dosimetry, Lowest Observable Effect Levels, Performance-Incapacitation, and Possible Delayed Effects
DoD-056	Low-Level Sarin Neurotoxicity and Its Modulation by Pyridostigmine
DoD-057	Physiologic Effects of Stress in Gulf War Veterans
DoD-058	Illness Among Persian Gulf War Veterans: Case Validation Studies
DoD-059	Pyridostigmine-induced Neurodegeneration: Role of neuronal Apoptosis
DoD-060	Butyrylcholinesterase Genetic Variants in Persons with Gulf War Illness
DoD-061	Neurophysiologic and Neuropathologic Effects in Monkeys of Low Level Exposures to Sarin, Pyridostigmine, Pesticides, and Botulinum Toxoid
DoD-062	Sarin and Pyridostigmine Interaction under Physical Stress: Neurotoxic Effects in Mice
DoD-063	PGW Veterans: Epidemiological and Clinical Evidence for Residual Organophosphate Neurotoxicity
DoD-064	Individual Differences in Neurobehavioral Effects of Pyridostigmine
DoD-065	Multi-disciplinary Pathophysiologic Studies of Neurotoxic Gulf War Related Syndromes Leading to Diagnosis and Treatment

DoD-066	Testing for mycoplasmal infection replicability of nucleoprotein gene tracking and forensic polymerase chain reaction
DoD-067	Antibacterial Treatment Method Based Upon the Excretion of Dead and Decaying Spherical Bacteria
DoD-069	Five-Year Follow-Up of Army Personnel Exposed to Chemical Warfare Agents
DoD-070	War Syndromes from 1900 to the Present: Symptom Patterns and Long-term Health Outcomes
DoD-071	A Comparison of Post Deployment Hospitalization Between Vietnam and Gulf War Veterans
DoD-072	Long-term Effects of Subchronic Exposure to Sarin, Alone and with Stress or Other Chemicals
DoD-073	Post-deployment Morbid Stress, Behavior and Health: Developing a Model for Predicting Morbidity, Mortality, and other Adverse Outcomes
DoD-074	Relationship of Stress Exposures to Health in Gulf War Veterans
DoD-075	Toxic Interactions of Prophylactic Drugs and Pesticides
DoD-076	Evaluations of Immunotoxicity due to Concurrent Exposure to DEET, Pyridostigmine, and JP-8 Jet Fuel
DoD-077	Percutaneous Absorption of Chemical Mixtures Relevant to the Gulf War
DoD-078	Experimental Models of Gulf War Syndrome
DoD-079	Time Course of Stress-induced Impairment of Blood Brain Barrier
DoD-080	Molecular Regulation of Corticosteroid Receptor Expression in Stress-Responsive Cells
DoD-081	Immunotoxicity due to Coexposure to DEET, Pyridostigmine, and Stress
DoD-082	Feasibility of Developing a Registry of PTSD Affected Veteran Sib Pairs
DoD-083	Risk for Stress-related Substance Abuse: the Effects of Family History of Alcoholism
DoD-084	Psychobiologic Alterations in Persian Gulf War Veterans with and without PTSD
DoD-085	CNS Cytokines and CRH in Gulf War Veterans with Multiple Unexplained Symptoms
DoD-086	Effects of Combat Stress on Structure and Function of the Hippocampus
DoD-087	Measurement and Validation of Psychosocial Risk and Resilience Factors Accounting for Physical and Mental Health and Health-Related Quality of Life among PGWVs
DoD-088	Clinical Relevance of Novel Immunological Markers in PTSD
DoD-089	Limbic Blood Flow and Opiate Receptor PET in Posttraumatic Stress Disorder

DoD-090	SPECT Benzodiazepine Receptor and MR Imaging in PTSD
DoD-091	Neurological and Circadian Substrates of PTSD-like Behaviors
DoD-092	Traumatic Experiences Persistently Enhance Cue-dependent Learning: Toward an Animal Model of Chronic Stress and Posttraumatic Stress Disorder
DoD-093	Troops Exposed to Nerve Agents at Aberdeen Proving Ground: Follow-Up
DoD-094	Combined Analysis of the VA and DoD Gulf War Clinical Registries: A Study of Clinical Findings from Systematic Medical Examinations of 100,000 U.S. Gulf War Veterans
DoD-095	Development of Diagnostic tools and alternative treatment drugs for Leishmania
DoD-096	Deployment Health Center
DoD-097	Surveillance of B. pertussis among Military Trainees with Respiratory Disease: Development and Validation of a Highly Sensitive PCR and Beacon Probe based Method for Diagnosis of Pertussis
DoD-098	Investigation of a Baseline Medical Database to Evaluate the Health of Military Forces and Veterans
DoD-099	DoD-wide Medical Surveillance for Potential Long-Term Adverse Events associated with Anthrax Immunization in Active Duty Service Members, Proposal 1: Hospitalizations
DoD-100	Antibodies to Squalene
DoD-101	Mechanisms in Chronic Multisymptom Illnesses
DoD-102	Case-Control Study of Fatal Motor Vehicle Crashes Among Gulf War and Non-Deployed Veterans
DoD-103	Human Metabolism and Interactions of Deployment-related Chemicals
DoD-104	Clinical Evaluation of a Proposed New Gulf War Syndrome
DoD-105	Neuroplasticity and Calcium Signaling in Stressed Rat Amygdala
DoD-106	The Role of Th1/Th2 cytokine balance in Gulf War-related illness
DoD-107	Stress, Organophosphates and Blood Brain Barrier Integrity
DoD-108	Health Status of Current National Guard Members
DoD-109	Disordered Responses to Orthostatic Stress in the Pathogenesis of Gulf War Syndrome Symptoms
DoD-110	Predictors of Career and Family Dysfunction in Young Adults Enlisting in the United States Navy
DoD-111	Autonomic Dysfunction in Gulf War Veterans

DoD-112	Role of Respirable Saudi Arabian Sand and Pyridostigmine in the Gulf War Syndrome: An Autoimmune Adjuvant Disease?
DoD-113	Interactions of Subsymptomatic Doses of Sarin with Pyridostigmine: Neurochemical, Behavioral, and Physiological Effects
DoD-114	A Re-examination of Neuropsychological Functioning in Persian Gulf War Veterans
DoD-115	A Randomized, Multi-Center, Controlled Trial of Multi-Model Therapy in Veterans with Gulf War Illnesses (EBT) (See also VA-62; formerly VA/DoD 1D)
DoD-116	VA/DoD Core Funding of the Medical Follow-Up Agency (See also VA-63; formerly VA-DoD-2D/2V)
DoD-116A	Follow-Up Investigation of Troops Exposed to Nerve Agents at Aberdeen Proving Ground (Pilot Study) (See also VA-63A; formerly VA/DoD-2DA)
DoD-116B	Patterns of Pre-Persian Gulf War Illness and Health Care Seeking, Pilot Study (See also VA-63B; formerly VA/DoD- 2DB)
DoD-117	Patterns of Pre-Persian Gulf War Illness and Health Care Seeking
DoD-118	An Epidemiological Investigation into the Occurrence of Amyotrophic Lateral Sclerosis (ALS) Among Gulf War Veterans (See also VA-61)
DoD-119	Antibiotic Treatment of Gulf War Veterans' Illnesses (ABT) (See also VA-55)
DoD-120	Assessing the Potential Health Impact of the Gulf War on Saudi Arabia National Guard Members and Their Dependents
DoD-121	Evaluation of the Health Risks of Embedded Depleted Uranium Shrapnel During Pregnancy and Offspring Development
DoD-122	Carcinogenic Potential of Depleted Uranium and Tungsten Alloys
DoD-123	Immunotoxicity of Depleted Uranium and Heavy Metal Tungsten Alloys
DoD-124	Randomized, Controlled Trial for Combination Treatment with Pyridostigmine, DEET, and Permethrin
DoD-125	A Randomized Clinical Trial of Cognitive-Behavioral Treatment for PTSD in Women (See VA-74)
DoD-126	Blood-Brain Barrier Transport of Uranium
DoD-127	Depleted Uranium Fragment Carcinogenicity: Extrapolation of Findings in Rodents to Man
DoD-128	Multifactorial Assessment of Depleted Uranium Neurotoxicity
DoD-129	Inhalation of Uranium Oxide Aerosol: CNS Deposition, Neurotoxicity, and Role in Gulf War Illness

DoD-130	Carcinogenicity and Immunotoxicity of Embedded Depleted Uranium and Heavy-Metal Tungsten Alloys in Rodents
DoD-131	Magnetic Resonance and Spectroscopy of the Human Brain in Gulf War Illnesses
DoD-132	Impaired Auditory Sensory Gating, Acoustic Startle Response: Effects of Long and Short Deployments on Army Combat Readiness
DoD-133	Odors, Deployment Stress, and Health: A Conditioning Analysis of Gulf War Syndrome
DoD-134	Identification and Development of Biological Markers of Human Exposure to the Insecticide Permethrin
DoD-135	Biochemical Markers for Exposure to Low Doses of Organophosphorous Exposure
DoD-136	A Mechanism-Based, Molecular Fingerprint Strategy for Detecting Biomarkers of Organophosphate Exposure
DoD-137	Low Level Exposure to Sulfur Mustard: Development of a SOP for Analysis of Albumin Adducts and of a System for Non-Invasive Diagnosis on Skin
DoD-138	Improving Blood Monitoring of Enzymes as Biomarkers of Risk from Anticholinergic Pesticides and Chemical Warfare Agents
DoD-139	Assessment of the Role of Stress-Activated Kinase in the Pathogenesis of Gulf War Illnesses
DoD-140	US Department of Defense Surveillance for Neoplasms in Infancy
DoD-141	Physical, Mental, Social, and Family Health Outcomes of Gulf War Veterans
DoD-142	Illnesses Among Persian Gulf War Veterans: Case Validation Studies (Iowa / Great Britain)
DoD-143	Millennium Cohort Study (See also VA-78)
DoD-144	Psychological Health Screening: Methods and Metrics for Deployed Forces
DoD-145	Early Intervention Research Program to Enhance Soldier Resilience
DoD-146	Assessment of Toxicology Assays Methods & Chemical Exposures Among a Cohort of US Marines
DoD-147	Development and Validation of the Automated Neuropsychological Assessment Metric (ANAM) for Deployment Health Monitoring Applications
DoD-148	Predicting operational readiness for deployed Army National Guard and Army Reserve soldiers and families
DoD-149	Longitudinal Health Study of Gulf War Veterans
DoD-150	Validation Study of Gulf War Deployment Files
DoD-151	Mechanisms and Consequences of Vaccine Effects on Th1/Th2 Balance in Gulf War

	Veterans
DoD-152	Characterization of Intracellular Signaling Pathways Activated by Nerve Agents
DoD-153	Gulf War Illness Research
DoD-154	Prospective Assessment of Neurocognition in Future Gulf-deployed and Gulf-nondeployed Military Personnel: A Pilot Study (See also VA-88)
DoD-155	Neuropsychological Functioning in Gulf War Veterans Exposed to Pesticides and Pyridostigmine Bromide
DoD-156	The Effects of Diesel Exhaust and Stress on the Acute Phase Response and Symptoms in the Chemically Intolerant

DEPARTMENT OF HEALTH AND HUMAN SERVICES PROJECTS

HHS-001	Health Assessment of Persian Gulf War Veterans from Iowa
HHS-002	Disease Cluster in a Pennsylvania Air National Guard Unit, EPI-AID 95-18
HHS-003	Biomarkers of Susceptibility and Polycyclic Aromatic Hydrocarbon (PAH) Exposure in Urine and Blood Cell DNA from U.S. Army Soldiers Exposed to Kuwaiti Oil Well Fires
HHS-004	Suspected Increase of Birth Defects and Health Problems Among Children Born to Persian Gulf War Veterans In Mississippi
HHS-005	Cognitive Function and Symptom Patterns in Persian Gulf Veterans
HHS-006	Defining Gulf War Illness
HHS-007	Immunotoxicity of Dermal Permethrin and Cis-Urocanic Acid
HHS-008	Strategy to Identify Non-Additive Response to Chemical Mixtures
HHS-009	Improving Health Risk Communications to Prevent Unexplained Illnesses Related to Military Deployments
HHS-010	Health-e Voice: Optimized Implementation of a Stepped Clinical Risk Communications Guideline
HHS-011	Deployment to the Gulf War and the Subsequent Development of Cancer
HHS-012	Epidemiology of ALS in Veterans

DEPARTMENT OF VETERANS AFFAIRS PROJECTS

VA-001	Mortality Follow-up Study of Persian Gulf Veterans
VA-002	National Health Survey of Persian Gulf Veterans
VA-002A	VA National Survey of Persian Gulf Veterans - Phase I
VA-002B	VA National Survey of Persian Gulf Veterans - Phase II
VA-002C	VA National Survey of Persian Gulf Veterans - Phase III
VA-003	Use of Roster of Veterans Who Served in Persian Gulf Area
VA-004	Boston Environmental Hazards Research Center Program
VA-004A	Evaluation of Cognitive Functioning of Persian Gulf Veterans
VA-004B	Evaluation of Neurological Functioning in Persian Gulf Veterans
VA-004C	Gulf War And Vietnam Veterans Cancer Incidence Surveillance
VA-004D	Evaluation of Respiratory Dysfunction Among Gulf War Veterans
VA-004E	The Aromatic Hydrocarbon Receptor (AhR) as a Biomarker of Susceptibility
VA-004F	Validity of Computerized Tests
VA-005	East Orange Environmental Hazards Research Center Program
VA-005A	Health and Exposure Survey of Persian Gulf Veterans
VA-005B	Physiological and Psychological Assessments of Persian Gulf Veterans
VA-005C	Effects of Exertion and Chemical Stress on Persian Gulf Veterans
VA-005D	Effects of Genetics and Stress on Responses to Environmental Toxins
VA-006	Core Program: Portland Environmental Hazards Research Center: Environment, Veterans Health and the Gulf War Syndrome. Core Project for Clinical and Epidemiology Research
VA-006A	Psychosocial, Neuropsychological and Neurobehavioral Assessment (Project I)
VA-006B	Clinical and Neuroendocrine Aspects of Fibromyalgia (Project II)
VA-006C	Neurotoxicity of Environmental Pollutants and Warfare Agents (Project III)
VA-006D	DNA Damage from Chemical Agents and Its Repair (Project IV)
VA-006E	Clinical and Epidemiology Leishmania Research

VA-007	Desert Storm Reunion Survey
VA-008	Psychological Test Data of Gulf War Veterans Over Time
VA-009	Evaluation of Cognitive Functioning in Persian Gulf War Veterans Reporting War-related Health Problems
VA-010	Memory and Attention in PTSD
VA-011	Neuropsychological Functioning in Veterans
VA-012	Psychological Assessment of Operation Desert Storm Returnees
VA-013	Neurobehavioral Aspects of Persian Gulf Experiences: A Pilot Study
VA-015	Vaccine-Mediated Immunity Against Leishmaniasis
VA-016	Protective Immunity in Experimental Visceral Leishmaniasis
VA-017	Immunological Evaluation of Persian Gulf Veterans
VA-018	Chronic Gastrointestinal Illness in Persian Gulf Veterans
VA-020	Psychological Adjustment in Operation Desert Shield/Storm Veterans
VA-021	A Comparison of PTSD Symptomatology among Three Army Medical Units Involved in ODS
VA-036	Stress Symptoms and Their Causal Attribution in Desert Storm Veterans
VA-040	Musculoskeletal Symptoms in Gulf War Syndrome
VA-046	Diarrhea in Persian Gulf Veterans: An Irritable Bowel-Like Disorder
VA-047	Retrospective Verification of Mustard Gas Exposure
VA-048	Cross-Sensitization as a CNS Model for Gulf War Chemical Intolerance
VA-049	Sensitivity to Pyridostigmine Bromide: Persistent Neural Dysfunction
VA-050	Neuropsychological findings in a sample of Operation Desert Storm veterans
VA-051	Psychobiological Assessment of Desert Storm Veterans
VA-053	Spouses and Children Program
VA-054	Follow-up of Psychological and Neurocognitive Gulf War Outcome: Relation to Stress
VA-055	Antibiotic Treatment of Gulf War Veterans' Illnesses (ABT) (See also DoD-119)
VA-056	Birmingham's Gulf War Veterans' Illness Demonstration Clinic (13)

VA-057	Case Management and Residential Rehabilitation for Persian Gulf War Veterans (13)
VA-058	Implementation and Evaluation of Gulf War Veterans' Demonstration Project (13)
VA-059	Demonstration Treatment Program for Gulf War Veterans With Unexplained Physical Symptoms (13)
VA-060	Identification and Management of Sleep Disorders in Gulf War Veterans
VA-061	An Epidemiological Investigation into the Occurrence of Amyotrophic Lateral Sclerosis (ALS) Among Gulf War Veterans (See also DoD-118)
VA-062	A Randomized, Multi-Center, Controlled Trial of Multi-Model Therapy in Veterans with Gulf War Illness (EBT) (See also DoD-115; formerly VA/DoD 1V)
VA-063	VA/DoD Core funding of the Medical Follow-Up Agency (See also DoD-116; formerly VA/DoD-2V/2D)
VA-063A	Follow-Up Investigation of troops exposed to nerve agents at Aberdeen Proving Ground (Pilot Study) (See also DoD-116A; formerly VA/DoD-2VA/2DA)
VA-063B	Patterns of Pre-Persian Gulf War Illness and Health Care Seeking Pilot Study (See also DoD-116B; previously VA/DoD-2VB)
VA-064	Boston Environmental Hazards Research Center
VA-064A	Functional Neuroimaging in Lead Exposed Adults
VA-064B	Quantification and Validation of Structure-Function relationships through visuospatial test performance
VA-064C	Development of a structured neurotoxicant assessment checklist (SNAC) for clinical use in veteran populations
VA-065	San Antonio Environmental Hazards Research Center
VA-065A	Does a variant of the human SOD2 gene increase sensitivity to hazards?
VA-065B	The contribution of FEN-1 to genetic integrity subsequent to oxidative stress
VA-065C	The importance of hydrogen peroxide detoxification in cellular protection
VA-065D	Do defective Gpx1 and ALDH2 genes increase sensitivity to environmental hazards?
VA-066	Physiological Responding in Posttraumatic Stress Disorder
VA-067	Olfactory Functioning in Gulf War Veterans
VA-068	Family Study of Fibromyalgia
VA-069	Cardiovascular Hyporeactivity and Fatiguing Illness in Gulf War Veterans

VA-070	A Clinical Evaluation of the Health Status of Persian Gulf War Veterans in VISN 8
VA-071	Central Nervous System Modulation of Visceral Pain in the Persian Gulf Syndrome
VA-072	Roles of Paraoxonase, Butyrylcholinesterase and Stress in Unexplained Illnesses
VA-073	Pain Sensitivity in Gulf War Veterans with Medically Unexplained Musculoskeletal Pain
VA-074	A Randomized Clinical Trial for Cognitive-Behavioral Treatment for PTSD in Women (See DoD-125)
VA-075	ALS and Veterans: Are Veterans at Increased Risk?
VA-076	Analysis of Hippocampal Volume in Aging Combat Veterans with PTSD
VA-077	HPA Axis Reactivity in Men and Women with Chronic PTSD
VA-078	Millennium Cohort Study (See also DoD-143)
VA-080	Neurochemical and Neurobehavioral Impact of Pyridostigmine Bromide Treatment and Stress
VA-081	Stress, Pro-Inflammatory Cytokines and Coping Behavior
VA-082	Pituitary Adrenal Function in People with Fatiguing Illness
VA-083	Neuropsychological Assessment of a Population-Based Sample of Persian Gulf War Veterans and Controls
VA-084	Neurobiology of Severe Psychological Trauma in Women
VA-085	Associative Learning in Veterans with and without Combat Experience
VA-086	A Clinical Trial of Magnetic Stimulation in Depression
VA-087	Improving Outcomes of Depression in Primary Care
VA-088	Prospective Assessment of Neurocognition in Future Gulf-deployed and Gulf-nondeployed Military Personnel: A Pilot Study (See also DoD-154)
VA-089	National Registry of Veterans with Amyotrophic Lateral Sclerosis
VA-090	Differential Gene Expression in Pathologies Associated with Neuronal Hyperexcitability: Links to Gulf War Illness
VA-090A	Neuronal Hyperexcitability and Motor Neuron Regeneration
VA-090B	Gene Expression and Proteomic Strategies in Severe Psychiatric Disorders
VA-090C	Developmental Differences in Alcohol Withdrawal Sensitivity
VA-090D	Seizures and Neuroplasticity: Physiology and Biochemistry

VA-091	The Role of Dietary Choline in Neuroprotection
VA-092	Acetylcholinesterase Activity In Gulf War Veterans
VA-093	HPA Axis Alterations in PTSD: A Comparison of Gulf War and Vietnam Veterans
VA-094	The Immunology of Chronic Cutaneous Leishmaniasis
VA-095	The Role of Signal Regulatory Proteins in Astrocytomas
VA-096	Functional Imaging of Pain in Veterans with Unexplained Muscle Pain
VA-097	Improving a mM-CSF Tumor Vaccine for Established Intracranial Gliomas
VA-098	Post-Transcriptional Gene Regulation of VEGF in Malignant Gilomas
VA-099	Vaccination Against Visceral Leishmaniasis with a multi-epitope vaccine
VA-100	Studies of the Blood-Brain Barrier and its Manipulation
VA-101	Biomarkers Discovery in ALS
VA-102	Cholinergic and Monoaminergic Influences on Sleep
VA-103	Hypothalamic and Basal Forebrain Regulation of Sleep and Arousal
VA-104	Characterization of Pain Processing Mechanisms in the Irritable Bowel Syndrome
VA-105	Expression of the Major Surface Protease of Leishmania Chagasi

Appendix B

Project List by Research Focus Areas

Brain and Nervous System Function

Clinical

Research Focus	Project Focus	Project	Project Title
Environmental Toxicology	Symptoms; Exposure;	VA-064A	Functional Neuroimaging in Lead Exposed Adults
Environmental Toxicology; Chemical Weapons	Symptoms	DoD-063	PGW Veterans: Epidemiological and Clinical Evidence for Residual Organophosphate Neurotoxicity
Immune Function and Infectious Diseases; Symptoms and General Health	Symptoms	VA-005B	Physiological and Psychological Assessments of Persian Gulf Veterans
Symptoms and General Health	Diagnosis	DoD-032	Neuropsychological Functioning in Persian Gulf Era Veterans
Symptoms and General Health	Symptoms	DoD-040	Psychological and Neurobiological Consequences of the Gulf War Experience
Symptoms and General Health	Prevention	DoD-083	Risk for Stress-related Substance Abuse: the Effects of Family History of Alcoholism
Symptoms and General Health	Symptoms	DoD-084	Psychobiologic Alterations in Persian Gulf War Veterans with and without PTSD
Symptoms and General Health	Symptoms	DoD-086	Effects of Combat Stress on Structure and Function of the Hippocampus
Symptoms and General Health	Symptoms	DoD-089	Limbic Blood Flow and Opiate Receptor PET in Posttraumatic Stress Disorder
Symptoms and General Health	Diagnosis	DoD-090	SPECT Benzodiazepine Receptor and MR Imaging in PTSD
Symptoms and General Health	Symptoms	DoD-132	Impaired Auditory Sensory Gating, Acoustic Startle Response: Effects of Long and Short Deployments on Army Combat Readiness
Symptoms and General Health	Diagnosis	DoD-147	Development and Validation of the Automated Neuropsychological Assessment Metric (ANAM) for Deployment Health Monitoring Applications
Symptoms and General Health	Symptoms	HHS-005	Cognitive Function and Symptom Patterns in Persian Gulf Veterans
Symptoms and General Health	Symptoms	VA-004	Boston Environmental Hazards Research Center Program
Symptoms and General Health	Symptoms	VA-004A	Evaluation of Cognitive Functioning of Persian Gulf Veterans
Symptoms and General Health	Symptoms	VA-004B	Evaluation of Neurological Functioning in Persian Gulf Veterans
Symptoms and General Health	Diagnosis	VA-004F	Validity of Computerized Tests
Symptoms and General Health	Symptoms	VA-005	East Orange Environmental Hazards Research Center Program

Brain and Nervous System Function

Clinical

Research Focus	Project Focus	Project	Project Title
Symptoms and General Health	Symptoms	VA-006A	Psychosocial, Neuropsychological and Neurobehavioral Assessment (Project I)
Symptoms and General Health	Symptoms	VA-007	Desert Storm Reunion Survey
Symptoms and General Health	Symptoms	VA-009	Evaluation of Cognitive Functioning in Persian Gulf War Veterans Reporting War-related Health Problems
Symptoms and General Health	Symptoms	VA-010	Memory and Attention in PTSD
Symptoms and General Health	Symptoms	VA-011	Neuropsychological Functioning in Veterans
Symptoms and General Health	Symptoms	VA-012	Psychological Assessment of Operation Desert Storm Returnees
Symptoms and General Health	Symptoms	VA-013	Neurobehavioral Aspects of Persian Gulf Experiences: A Pilot Study
Symptoms and General Health	Symptoms	VA-020	Psychological Adjustment in Operation Desert Shield/Storm Veterans
Symptoms and General Health	Symptoms	VA-021	A Comparison of PTSD Symptomatology among Three Army Medical Units Involved in ODS
Symptoms and General Health	Symptoms	VA-050	Neuropsychological findings in a sample of Operation Desert Storm veterans
Symptoms and General Health	Symptoms	VA-051	Psychobiological Assessment of Desert Storm Veterans
Symptoms and General Health	Symptoms	VA-054	Follow-up of Psychological and Neurocognitive Gulf War Outcome: Relation to Stress
Symptoms and General Health	Symptoms	VA-064	Boston Environmental Hazards Research Center
Symptoms and General Health	Symptoms	VA-066	Physiological Responding in Posttraumatic Stress Disorder
Symptoms and General Health	Symptoms	VA-072	Roles of Paraoxonase, Butyrylcholinesterase and Stress in Unexplained Illnesses
Symptoms and General Health	Symptoms	VA-076	Analysis of Hippocampal Volume in Aging Combat Veterans with PTSD
Symptoms and General Health	Symptoms	VA-077	HPA Axis Reactivity in Men and Women with Chronic PTSD
Symptoms and General Health	Symptoms	VA-083	Neuropsychological Assessment of a Population-Based Sample of Persian Gulf War Veterans and Controls
Symptoms and General Health	Symptoms	VA-084	Neurobiology of Severe Psychological Trauma in Women

Brain and Nervous System Function

Clinical

Research Focus	Project Focus	Project	Project Title
Symptoms and General Health	Symptoms	VA-085	Associative Learning in Veterans with and without Combat Experience
Symptoms and General Health	Treatment	VA-089	National Registry of Veterans with Amyotrophic Lateral Sclerosis
Symptoms and General Health	Symptoms	VA-093	HPA Axis Alterations in PTSD: A Comparison of Gulf War and Vietnam Veterans
Symptoms and General Health	Symptoms; Diagnosis;	DoD-065	Multi-disciplinary Pathophysiologic Studies of Neurotoxic Gulf War Related Syndromes Leading to Diagnosis and Treatment
Symptoms and General Health	Symptoms; Exposure;	DoD-057	Physiologic Effects of Stress in Gulf War Veterans
Symptoms and General Health	Symptoms; Exposure;	DoD-133	Odors, Deployment Stress, and Health: A Conditioning Analysis of Gulf War Syndrome
Symptoms and General Health	Diagnosis; Symptoms;	DoD-087	Measurement and Validation of Psychosocial Risk and Resilience Factors Accounting for Physical and Mental Health and Health-Related Quality of Life among PGWVs
Symptoms and General Health	Treatment; Symptoms;	DoD-125	A Randomized Clinical Trial of Cognitive-Behavioral Treatment for PTSD in Women (See VA-74)
Symptoms and General Health	Diagnosis; Symptoms;	DoD-131	Magnetic Resonance and Spectroscopy of the Human Brain in Gulf War Illnesses
Symptoms and General Health	Diagnosis; Symptoms;	DoD-144	Psychological Health Screening: Methods and Metrics for Deployed Forces
Symptoms and General Health	Diagnosis; Symptoms;	DoD-153	Gulf War Illness Research
Symptoms and General Health	Treatment; Symptoms;	VA-060	Identification and Management of Sleep Disorders in Gulf War Veterans
Symptoms and General Health	Diagnosis; Symptoms;	VA-064B	Quantification and Validation of Structure-Function relationships through visuospatial test performance
Symptoms and General Health	Diagnosis; Symptoms;	VA-067	Olfactory Functioning in Gulf War Veterans
Symptoms and General Health	Treatment; Symptoms;	VA-074	A Randomized Clinical Trial for Cognitive-Behavioral Treatment for PTSD in Women (See DoD-125)
Symptoms and General Health	Treatment; Symptoms;	VA-086	A Clinical Trial of Magnetic Stimulation in Depression
Symptoms and General Health	Treatment; Symptoms;	VA-087	Improving Outcomes of Depression in Primary Care
Symptoms and General Health; Environmental Toxicology	Symptoms; Exposure;	VA-008	Psychological Test Data of Gulf War Veterans Over Time

Brain and Nervous System Function

Development

Research Focus	Project Focus	Project	Project Title
Symptoms and General Health	Treatment; Prevention;	VA-097	Improving a mM-CSF Tumor Vaccine for Established Intracranial Gliomas
Symptoms and General Health	Diagnosis; Symptoms;	VA-101	Biomarkers Discovery in ALS

Brain and Nervous System Function

Epidemiology

Research Focus	Project Focus	Project	Project Title
	Symptoms	VA-061	An Epidemiological Investigation into the Occurrence of Amyotrophic Lateral Sclerosis (ALS) Among Gulf War Veterans (See also DoD-118)
	Treatment; Prevention;	DoD-145	Early Intervention Research Program to Enhance Soldier Resilience
Symptoms and General Health	Symptoms	DoD-023	Acute and Long-Term Impact of Deployment to Southwest Asia on the Physical and Mental Health of Soldiers and their
Symptoms and General Health	Symptoms	DoD-082	Feasibility of Developing a Registry of PTSD Affected Veteran Sib Pairs
Symptoms and General Health	Symptoms	DoD-114	A Re-examination of Neuropsychological Functioning in Persian Gulf War Veterans
Symptoms and General Health	Symptoms	DoD-118	An Epidemiological Investigation into the Occurrence of Amyotrophic Lateral Sclerosis (ALS) Among Gulf War Veterans (See also VA-61)
Symptoms and General Health	Symptoms	HHS-006	Defining Gulf War Illness
Symptoms and General Health	Symptoms	HHS-012	Epidemiology of ALS in Veterans
Symptoms and General Health	Symptoms	VA-036	Stress Symptoms and Their Causal Attribution in Desert Storm Veterans
Symptoms and General Health	Symptoms	VA-068	Family Study of Fibromyalgia
Symptoms and General Health	Symptoms	VA-075	ALS and Veterans: Are Veterans at Increased Risk?
Symptoms and General Health	Symptoms; Diagnosis;	DoD-104	Clinical Evaluation of a Proposed New Gulf War Syndrome
Symptoms and General Health	Diagnosis; Symptoms;	DoD-052	Female Gender and Other Potential Predictors of Functional Health Status Among Persian Gulf War Veterans

Brain and Nervous System Function

Epidemiology

Research Focus	Project Focus	Project	Project Title
Symptoms and General Health	Diagnosis; Symptoms;	DoD-154	Prospective Assessment of Neurocognition in Future Gulf-deployed and Gulf-nondeployed Military Personnel: A Pilot
Symptoms and General Health	Diagnosis; Symptoms;	HHS-002	Disease Cluster in a Pennsylvania Air National Guard Unit, EPI-AID 95-18
Symptoms and General Health	Diagnosis; Symptoms;	VA-088	Prospective Assessment of Neurocognition in Future Gulf-deployed and Gulf-nondeployed Military Personnel: A Pilot

Brain and Nervous System Function

Mechanistic

Research Focus	Project Focus	Project	Project Title
	Symptoms	VA-091	The Role of Dietary Choline in Neuroprotection
Symptoms and General Health	Symptoms	DoD-080	Molecular Regulation of Corticosteroid Receptor Expression in Stress-Responsive Cells
Symptoms and General Health	Symptoms	DoD-091	Neurological and Circadian Substrates of PTSD-like Behaviors
Symptoms and General Health	Symptoms	DoD-092	Traumatic Experiences Persistently Enhance Cue-dependent Learning: Toward an Animal Model of Chronic Stress and Posttraumatic Stress Disorder
Symptoms and General Health	Symptoms	DoD-105	Neuroplasticity and Calcium Signaling in Stressed Rat Amygdala
Symptoms and General Health	Symptoms	VA-081	Stress, Pro-Inflammatory Cytokines and Coping Behavior
Symptoms and General Health	Symptoms	VA-090	Differential Gene Expression in Pathologies Associated with Neuronal Hyperexcitability: Links to Gulf War Illness
Symptoms and General Health	Symptoms	VA-090A	Neuronal Hyperexcitability and Motor Neuron Regeneration
Symptoms and General Health	Symptoms	VA-090B	Gene Expression and Proteomic Strategies in Severe
Symptoms and General Health	Symptoms	VA-090C	Developmental Differences in Alcohol Withdrawal Sensitivity
Symptoms and General Health	Symptoms	VA-090D	Seizures and Neuroplasticity:Physiology and Biochemistry
Symptoms and General Health	Symptoms	VA-092	Acetylcholinesterase Activity In Gulf War Veterans

Brain and Nervous System Function

Mechanistic

Research Focus	Project Focus	Project	Project Title
			Psychiatric Disorders
Symptoms and General Health	Symptoms	VA-095	The Role of Signal Regulatory Proteins in Astrocytomas
Symptoms and General Health	Symptoms	VA-098	Post-Transcriptional Gene Regulation of VEGF in Malignant Gilomas
Symptoms and General Health	Symptoms	VA-103	Hypothalamic and Basal Forebrain Regulation of Sleep and Arousal
Symptoms and General Health	Treatment; Symptoms;	VA-100	Studies of the Blood-Brain Barrier and its Manipulation
Symptoms and General Health	Prevention; Symptoms;	VA-102	Cholinergic and Monoaminergic Influences on Sleep

Environmental Toxicology

Clinical

Research Focus	Project Focus	Project	Project Title
Brain and Nervous System Function	Interactions; Exposure; Symptoms	VA-048	Cross-Sensitization as a CNS Model for Gulf War Chemical Intolerance
Brain and Nervous System Function; Symptoms and General Health	Exposure; Symptoms;	VA-005C	Effects of Exertion and Chemical Stress on Persian Gulf Veterans
Chemical Weapons	Symptoms	DoD-060	Butyrylcholinesterase Genetic Variants in Persons with Gulf War Illness
Chemical Weapons	Exposure	DoD-146	Assessment of Toxicology Assay Methods and Chemical Exposures Among a Cohort of US Marines Deployed in the Gulf War
Pyridostigmine Bromide	Exposure; Prevention;	DoD-011	Male/Female Differential Tolerances to Pyridostigmine Bromide
Pyridostigmine Bromide; Brain and Nervous System Function	Exposure; Interactions;	DoD-124	Randomized, Controlled Trial for Combination Treatment with Pyridostigmine, DEET, and Permethrin
Pyridostigmine Bromide; Brain and Nervous System Function	Exposure; Interactions;	DoD-155	Neuropsychological Functioning in Gulf War Veterans Exposed to Pesticides and Pyridostigmine Bromide
Pyridostigmine Bromide; Brain and Nervous System Function	Exposure; Symptoms;	DoD-064	Individual Differences in Neurobehavioral Effects of Pyridostigmine

Environmental Toxicology

Clinical

Research Focus	Project Focus	Project	Project Title
Symptoms and General Health	Exposure; Symptoms;	VA-004 D	Evaluation of Respiratory Dysfunction Among Gulf War Veterans
Symptoms and General Health; Brain and Nervous System Function	Exposure; Symptoms;	DoD-156	The Effects of Diesel Exhaust and Stress on the Acute Phase Response and Symptoms in the Chemically Intolerant

Environmental Toxicology

Development

Research Focus	Project Focus	Project	Project Title
	Interactions; Exposure;	DoD-034	Characterization of Emissions from Heaters Burning Leaded Diesel Fuel in Unvented Tents
	Diagnosis; Exposure;	DoD-134	Identification and Development of Biological Markers of Human Exposure to the Insecticide Permethrin
	Exposure; Interactions;	HHS-008	Strategy to Identify Non-Additive Response to Chemical Mixtures
Brain and Nervous System Function; Symptoms and General Health	Diagnosis; Exposure; Symptoms	VA-064C	Development of a structured neurotoxicant assessment checklist (SNAC) for clinical use in veteran populations
Chemical Weapons	Diagnosis	DoD-049	Diagnosis and Dosimetry of Exposure to Sulfur Mustard: Development of Standard Operating Procedures and Exploratory Research on Protein Adducts
Chemical Weapons	Exposure; Diagnosis;	DoD-138	Improving Blood Monitoring of Enzymes as Biomarkers of Risk from Anticholinergic Pesticides and Chemical Warfare Agents
Chemical Weapons	Diagnosis; Exposure;	DoD-050	Toxicokinetics of 0-Ethyl S-(2-Diisopropylaminoethyl) Methylphosphonothioate [(+)-VX] in Rats, Hairless Guinea Pigs and Marmosets - Identification of Metabolic Pathways
Chemical Weapons	Diagnosis; Exposure;	DoD-137	Low Level Exposure to Sulfur Mustard: Development of a SOP for Analysis of Albumin Adducts and of a System for Non-Invasive Diagnosis on Skin
Symptoms and General Health	Diagnosis; Exposure;	DoD-018	Kuwait Oil Fires Troop Exposure Assessment Model (TEAM)
Symptoms and General Health	Diagnosis; Exposure;	DoD-019	Persian Gulf Veterans Health Tracking System
Symptoms and General Health	Diagnosis; Exposure;	DoD-100	Antibodies to Squalene
Symptoms and General Health	Diagnosis; Exposure; Symptoms	DoD-016	Kuwait Oil Fire Health Risk Assessment

Environmental Toxicology

Epidemiology

Research Focus	Project Focus	Project	Project Title
Chemical Weapons	Exposure; Symptoms;	DoD-116A	Follow-Up Investigation of Troops Exposed to Nerve Agents at Aberdeen Proving Ground (Pilot Study) (See also VA-63A; formerly VA/DoD-2DA)
Chemical Weapons	Exposure; Symptoms;	VA-063A	Follow-Up Investigation of troops exposed to nerve agents at Aberdeen Proving Ground (Pilot Study) (See also DoD-116A; formerly VA/DoD-2VA/2DA)
Chemical Weapons; Symptoms and General Health	Exposure; Symptoms;	DoD-069	Five Year Follow-Up of Army Personnel Exposed to Chemical Warfare Agents
Chemical Weapons; Symptoms and General Health	Exposure; Symptoms;	DoD-093	Troops Exposed to Nerve Agents at Aberdeen Proving Ground: Follow-Up
Pyridostigmine Bromide	Exposure	DoD-017	Retrospective Studies Involving Military Use of Pyridostigmine as a Pretreatment for Nerve Agent Poisoning
Pyridostigmine Bromide	Prevention; Exposure;	DoD-021	Study of Variability In Pyridostigmine Inhibition of Blood Cholinesterases in Healthy Adults and Individuals With Symptoms Following Participation in Operation Desert Storm
Symptoms and General Health	Symptoms	DoD-013	Effects of Persian Gulf War Service on Military Working Dogs
Symptoms and General Health	Exposure; Symptoms;	DoD-094	Combined Analysis of the VA and DoD Gulf War Clinical Registries: A Study of Clinical Findings from Systematic Medical Examinations of 100,000 U.S. Gulf War Veterans
Symptoms and General Health	Exposure; Symptoms;	DoD-099	DoD-wide Medical Surveillance for Potential Long-Term Adverse Events associated with Anthrax Immunization in Active Duty Service Members, Proposal 1: Hospitalizations
Symptoms and General Health	Exposure; Symptoms;	VA-003	Use of Roster of Veterans Who Served in Persian Gulf Area
Symptoms and General Health	Exposure; Symptoms;	VA-006	Core Program: Portland Environmental Hazards Research Center: Environment, Veterans Health and the Gulf War Syndrome. Core Project for Clinical and Epidemiology

Environmental Toxicology

Mechanistic

Research Focus	Project Focus	Project	Project Title
	Exposure; Interactions;	DoD-103	Human Metabolism and Interactions of Deployment-related Chemicals

Environmental Toxicology

Mechanistic

Research Focus	Project Focus	Project	Project Title
	Exposure; Prevention;	HHS-003	Biomarkers of Susceptibility and Polycyclic Aromatic Hydrocarbon (PAH) Exposure in Urine and Blood Cell DNA from U.S. Army Soldiers Exposed to Kuwaiti Oil Well Fires
	Exposure; Prevention;	VA-004E	The Aromatic Hydrocarbon Receptor (AhR) as a Biomarker of Susceptibility
Brain and Nervous System Function; Chemical Weapons	Exposure; Symptoms;	DoD-022	Chronic Organophosphorus Exposure and Cognition
Brain and Nervous System Function; Immune Function and Infectious	Exposure; Interactions;	DoD-037	Neurobehavioral and Immunological Toxicity of Pyridostigmine, Permethrin, and DEET in Male and Female Rats
Brain and Nervous System Function;	Exposure	DoD-126	Blood-Brain Barrier Transport of Uranium
Brain and Nervous System Function;	Exposure; Symptoms;	DoD-128	Multifactorial Assessment of Depleted Uranium Neurotoxicity
Brain and Nervous System Function;	Exposure; Symptoms;	DoD-129	Inhalation of Uranium Oxide Aerosol: CNS Deposition, Neurotoxicity, and Role in Gulf War Illness
Brain and Nervous System Function; Symptoms and General Health	Exposure; Symptoms;	DoD-007A	Health Risk Assessment of Embedded Depleted Uranium: Behavior, Physiology, Histology, and Biokinetic Modeling
Chemical Weapons	Exposure; Diagnosis;	DoD-136	A Mechanism-Based, Molecular Fingerprint Strategy for Detecting Biomarkers of Organophosphate Exposure
Chemical Weapons; Brain and Nervous System Function	Exposure	VA-006D	DNA Damage from Chemical Agents and Its Repair (Project IV)
Chemical Weapons; Brain and Nervous System Function	Exposure; Diagnosis;	DoD-135	Biochemical Markers for Exposure to Low Doses of Organophosphorous Exposure
Chemical Weapons; Brain and Nervous System Function	Prevention; Exposure;	DoD-051	Transgenic Engineering of Cholinesterases: Tools for Exploring Cholinergic Responses
Chemical Weapons; Brain and Nervous System Function	Exposure; Interactions;	DoD-054	Assessment of Subchronic Neurobehavioral and Neuropathologic Effects in Rats Following Low-Level Sarin
Chemical Weapons; Brain and Nervous System Function	Exposure; Interactions;	DoD-055	Low-Level Exposure to GB Vapor in Air: Diagnosis/Dosimetry, Lowest Observable Effect Levels, Performance-Incapacitation, and Possible Delayed Effects
Chemical Weapons; Brain and Nervous System Function	Exposure; Interactions;	DoD-056	Low-Level Sarin Neurotoxicity and Its Modulation by Pyridostigmine
Chemical Weapons; Brain and Nervous System Function	Exposure; Interactions;	DoD-061	Neurophysiologic and Neuropathologic Effects in Monkeys of Low Level Exposures to Sarin, Pyridostigmine, Pesticides, and Botulinum Toxoid
Chemical Weapons; Brain and Nervous System Function	Exposure; Interactions;	DoD-062	Sarin and Pyridostigmine Interaction under Physical Stress: Neurotoxic Effects in Mice

Environmental Toxicology

Mechanistic

Research Focus	Project Focus	Project	Project Title
Chemical Weapons; Brain and Nervous System Function	Exposure; Interactions;	DoD-072	Long-term Effects of Subchronic Exposure to Sarin, Alone and with Stress or Other Chemicals
Chemical Weapons; Brain and Nervous System Function	Exposure; Interactions;	DoD-113	Interactions of Subsymptomatic Doses of Sarin with Pyridostigmine: Neurochemical, Behavioral, and Physiological Effects
Chemical Weapons; Brain and Nervous System Function	Exposure; Symptoms;	DoD-053	Long-Term Effects of Subclinical Exposures to Sarin
Chemical Weapons; Brain and Nervous System Function	Exposure; Symptoms;	DoD-152	Characterization of Intracellular Signaling Pathways Activated by Nerve Agents
Immune Function and Infectious Diseases	Exposure; Interactions;	HHS-007	Immunotoxicity of Dermal Permethrin and Cis-Urocanic Acid
Immune Function and Infectious Diseases	Exposure	DoD-123	Immunotoxicity of Depleted Uranium and Heavy Metal Tungsten Alloys
Immune Function and Infectious Diseases; Pyridostigmine Bromide	Exposure; Interactions;	DoD-077	Percutaneous Absorption of Chemical Mixtures Relevant to the Gulf War
Immune Function and Infectious Diseases; Symptoms and General Health	Exposure; Symptoms;	DoD-130	Carcinogenicity and Immunotoxicity of Embedded Depleted Uranium and Heavy-Metal Tungsten Alloys in Rodents
Pyridostigmine Bromide	Prevention; Exposure;	DoD-033	Effects of Pyridostigmine in Flinders Line Rats Differing in Cholinergic Sensitivity
Pyridostigmine Bromide	Exposure; Interactions;	DoD-010	Pyridostigmine Synergistic Toxicity Study
Pyridostigmine Bromide; Brain and Nervous System Function	Exposure; Interactions;	DoD-002	Physiological and Neurobehavioral Effects in Rodents from Exposure to Pyridostigmine, Fuels, and DEET
Pyridostigmine Bromide; Brain and Nervous System Function	Exposure; Interactions;	DoD-075	Toxic Interactions of Prophylactic Drugs and Pesticides
Pyridostigmine Bromide; Brain and Nervous System Function	Exposure; Interactions;	DoD-107	Stress, Organophosphates and Blood Brain Barrier Integrity
Pyridostigmine Bromide; Brain and Nervous System Function	Exposure; Interactions;	DoD-078	Experimental Models of Gulf War Syndrome
Pyridostigmine Bromide; Brain and Nervous System Function	Exposure; Interactions;	DoD-079	Time Course of Stress-induced Impairment of Blood Brain Barrier
Pyridostigmine Bromide; Brain and Nervous System Function	Exposure; Interactions;	DoD-139	Assessment of the Role of Stress-Activated Kinase in the Pathogenesis of Gulf War Illnesses
Pyridostigmine Bromide; Brain and Nervous System Function	Exposure; Interactions;	VA-006C	Neurotoxicity of Environmental Pollutants and Warfare Agents (Project III)

Environmental Toxicology

Mechanistic

Research Focus	Project Focus	Project	Project Title
Pyridostigmine Bromide; Brain and Nervous System Function	Exposure; Interactions;	VA-080	Neurochemical and Neurobehavioral Impact of Pyridostigmine Bromide Treatment and Stress
Pyridostigmine Bromide; Brain and Nervous System Function	Exposure; Symptoms;	DoD-059	Pyridostigmine-induced Neurodegeneration: Role of neuronal Apoptosis
Pyridostigmine Bromide; Brain and Nervous System Function	Exposure; Symptoms;	VA-049	Sensitivity to Pyridostigmine Bromide: Persistent Neural Dysfunction
Pyridostigmine Bromide; Symptoms and General Health	Exposure; Interactions;	VA-005D	Effects of Genetics and Stress on Responses to Environmental Toxins
Reproductive Health	Exposure; Symptoms;	DoD-121	Evaluation of the Health Risks of Embedded Depleted Uranium Shrapnel During Pregnancy and Offspring
Symptoms and General Health	Exposure	VA-065	San Antonio Environmental Hazards Research Center
Symptoms and General Health	Exposure	VA-065A	Does a variant of the human SOD2 gene increase sensitivity to hazards?
Symptoms and General Health	Exposure	VA-065B	The contribution of FEN-1 to genetic integrity subsequent to oxidative stress
Symptoms and General Health	Exposure	VA-065C	The importance of hydrogen peroxide detoxification in cellular protection
Symptoms and General Health	Exposure	VA-065D	Do defective Gpx1 and ALDH2 genes increase sensitivity to environmental hazards?
Symptoms and General Health;	Exposure	DoD-007B	Carcinogenicity of Depleted Uranium Fragments
Symptoms and General Health	Exposure; Symptoms;	DoD-122	Carcinogenic Potential of Depleted Uranium and Tungsten Alloys
Symptoms and General Health;	Exposure; Symptoms;	DoD-127	Depleted Uranium Fragment Carcinogenicity: Extrapolation of Findings in Rodents to Man

Immune Function and Infectious Diseases

Clinical

Research Focus	Project Focus	Project	Project Title
	Diagnosis	DoD-047	Study of Mycoplasmal Infections in Gulf War Veterans
	Symptoms	DoD-048	Assessment of Genomic Instability via Chromosome 7 Inversion Frequency in a Gulf-War Syndrome Cohort vs Selected Control Groups
	Diagnosis; Treatment;	VA-006E	Clinical and Epidemiology Leishmania Research
Brain and Nervous System Function	Symptoms	DoD-088	Clinical Relevance of Novel Immunological Markers in PTSD
Brain and Nervous System Function	Symptoms	VA-017	Immunological Evaluation of Persian Gulf Veterans
Environmental Toxicology	Exposure; Interactions;	DoD-106	The Role of Th1/Th2 cytokine balance in Gulf War-related illness
Symptoms and General Health	Treatment; Diagnosis;	DoD-067	Antibacterial Treatment Method Based Upon the Excretion of Dead and Decaying Spherical Bacteria
Symptoms and General Health	Symptoms; Exposure;	VA-006B	Clinical and Neuroendocrine Aspects of Fibromyalgia (Project II)
Symptoms and General Health	Exposure; Symptoms;	DoD-042	The Symptomatic Persian Gulf Veterans Protocol: An Analysis of Risk Factors with an Immunologic and Neuropsychiatric Assessment
Symptoms and General Health	Treatment; Symptoms;	DoD-119	Antibiotic Treatment of Gulf War Veterans' Illnesses (ABT) (See also VA-55)
Symptoms and General Health	Treatment; Symptoms;	VA-055	Antibiotic Treatment of Gulf War Veterans' Illnesses (ABT) (See also DoD-119)

Immune Function and Infectious Diseases

Development

Research Focus	Project Focus	Project	Project Title
	Diagnosis	DoD-008A	Serologic Diagnosis of Viscerotropic Leishmaniasis (VTL)
	Diagnosis	DoD-008B	Development of a Leishmania Skin Test Antigen (LSTA)
	Diagnosis	DoD-038	Diagnostic Antigens of Leishmania tropica
	Diagnosis	DoD-066	Testing for mycoplasmal infection replicability of nucleoprotein gene tracking and forensic polymerase chain reaction

Immune Function and Infectious Diseases

Development

Research Focus	Project Focus	Project	Project Title
	Diagnosis; Treatment;	DoD-095	Development of Diagnostic tools and alternative treatment drugs for Leishmania
Symptoms and General Health	Diagnosis	DoD-097	Surveillance of B. pertussis among Military Trainees with Respiratory Disease: Development and Validation of a Highly Sensitive PCR and Beacon Probe based Method for Diagnosis of Pertussis
Symptoms and General Health	Prevention; Symptoms;	VA-099	Vaccination Against Visceral Leishmaniasis with a multi-epitope vaccine

Immune Function and Infectious Diseases

Mechanistic

Research Focus	Project Focus	Project	Project Title
	Treatment	DoD-009	Identification of the Genetic Factors Which Control Tropism in Leishmania
	Prevention	VA-015	Vaccine-Mediated Immunity Against Leishmaniasis
	Prevention	VA-016	Protective Immunity in Experimental Visceral Leishmaniasis
	Prevention; Treatment;	VA-094	The Immunology of Chronic Cutaneous Leishmaniasis
Environmental Toxicology	Exposure	DoD-151	Mechanisms and Consequences of Vaccine Effects on Th1/Th2 Balance in Gulf War Veterans
Environmental Toxicology	Exposure; Interactions;	DoD-112	Role of Respirable Saudi Arabian Sand and Pyridostigmine in the Gulf War Syndrome: An Autoimmune Adjuvant Disease?
Environmental Toxicology; Pyridostigmine Bromide	Exposure; Interactions;	DoD-076	Evaluations of Immunotoxicity due to Concurrent Exposure to DEET, Pyridostigmine, and JP-8 Jet Fuel
Environmental Toxicology; Pyridostigmine Bromide	Exposure; Interactions;	DoD-081	Immunotoxicity due to Coexposure to DEET, Pyridostigmine, and Stress
Symptoms and General Health	Treatment; Symptoms;	VA-105	Expression of the Major Surface Protease of Leishmania Chagasi

Reproductive Health

Clinical

Research Focus	Project Focus	Project	Project Title
	Symptoms	VA-053	Spouses and Children Program
Environmental Toxicology; Chemical Weapons	Symptoms	VA-047	Retrospective Verification of Mustard Gas Exposure
Immune Function and Infectious Diseases	Symptoms	DoD-044	Investigation of Seminal Plasma Hypersensitivity Reactions

Reproductive Health

Epidemiology

Research Focus	Project Focus	Project	Project Title
	Prevention	DoD-001C	Epidemiologic Studies of Morbidity Among Gulf War Veterans: A Search for Etiologic Agents and Risk Factors; Study 3: A comparative study of pregnancy outcomes among Gulf War veterans and other active-duty personnel
	Prevention	DoD-001D	Epidemiologic Studies of Morbidity Among Gulf War Veterans: A Search for Etiologic Agents and Risk Factors; Study 4: Infertility and Miscarriage in Gulf War Veterans
	Symptoms	DoD-001G	Epidemiologic Studies of Morbidity Among Gulf War Veterans: A Search for Etiologic Agents and Risk Factors; Study 7: Prevalence of Congenital Anomalies Among Children of Persian Gulf War Veterans
	Prevention; Symptoms;	DoD-035	Feasibility of Investigating Whether There is a Relationship Between Birth Defects and Service in the Gulf War
	Prevention; Symptoms;	HHS-004	Suspected Increase of Birth Defects and Health Problems Among Children Born to Persian Gulf War Veterans In Mississippi

Symptoms and General Health

Clinical

Research Focus	Project Focus	Project	Project Title
	Symptoms	DoD-001A	Epidemiologic Studies of Morbidity Among Gulf War Veterans: A Search for Etiologic Agents and Risk Factors; A Study of Symptoms Among 1500 Seabees
	Diagnosis	DoD-109	Disordered Responses to Orthostatic Stress in the Pathogenesis of Gulf War Syndrome Symptoms

Symptoms and General Health

Clinical

Research Focus	Project Focus	Project	Project Title
	Symptoms	VA-018	Chronic Gastrointestinal Illness in Persian Gulf Veterans
	Symptoms	VA-040	Musculoskeletal Symptoms in Gulf War Syndrome
	Treatment; Symptoms;	VA-056	Birmingham's Gulf War Veterans' Illness Demonstration Clinic (13)
	Treatment; Symptoms;	VA-058	Implementation and Evaluation of Gulf War Veterans' Demonstration Project (13)
	Diagnosis; Symptoms;	VA-104	Characterization of Pain Processing Mechanisms in the Irritable Bowel Syndrome
Brain and Nervous System Function	Symptoms	DoD-036	Fatigue in Persian Gulf Syndrome-Physiologic Mechanisms
Brain and Nervous System Function	Symptoms	DoD-041	Evaluation of Muscle Function in Persian Gulf Veterans
Brain and Nervous System Function	Symptoms	DoD-058	Illness Among Persian Gulf War Veterans: Case Validation Studies
Brain and Nervous System Function	Symptoms	DoD-085	CNS Cytokines and CRH in Gulf War Veterans with Multiple Unexplained Symptoms
Brain and Nervous System Function	Symptoms	DoD-101	Mechanisms in Chronic Multisymptom Illnesses
Brain and Nervous System Function	Symptoms	VA-069	Cardiovascular Hyporeactivity and Fatiguing Illness in Gulf War Veterans
Brain and Nervous System Function	Symptoms	VA-071	Central Nervous System Modulation of Visceral Pain in the Persian Gulf Syndrome
Brain and Nervous System Function	Symptoms	VA-073	Pain Sensitivity in Gulf War Veterans with Medically Unexplained Musculoskeletal Pain
Brain and Nervous System Function	Symptoms	VA-082	Pituitary Adrenal Function in People with Fatiguing Illness
Brain and Nervous System Function	Symptoms	VA-096	Functional Imaging of Pain in Veterans with Unexplained Muscle Pain
Brain and Nervous System Function	Diagnosis; Symptoms;	DoD-111	Autonomic Dysfunction in Gulf War Veterans
Brain and Nervous System Function	Treatment; Symptoms;	DoD-115	A Randomized, Multi-Center, Controlled Trial of Multi-Model Therapy in Veterans with Gulf War Illnesses (EBT) (See also VA-62; formerly VA/DoD 1D)
Brain and Nervous System Function	Treatment; Symptoms;	VA-057	Case Management and Residential Rehabilitation for Persian Gulf War Veterans (13)

Symptoms and General Health

Clinical

Research Focus	Project Focus	Project	Project Title
Brain and Nervous System Function	Treatment; Symptoms;	VA-059	Demonstration Treatment Program for Gulf War Veterans With Unexplained Physical Symptoms (13)
Brain and Nervous System Function	Treatment; Symptoms;	VA-062	A Randomized, Multi-Center, Controlled Trial of Multi-Model Therapy in Veterans with Gulf War Illness (EBT) (See also DoD-115; formerly VA/DoD 1V)
Brain and Nervous System Function;	Diagnosis; Symptoms;	DoD-031	Dysregulation of the Stress Response in the Persian Gulf Syndrome

Symptoms and General Health

Epidemiology

Research Focus	Project Focus	Project	Project Title
	Symptoms	DoD-001B	Epidemiologic Studies of Morbidity Among Gulf War Veterans: A Search for Etiologic Agents and Risk Factors; Study 2: A Comparative Study of Hospitalizations among Active-Duty Personnel Who Participated in the Gulf War and Similar Personnel Who Did Not.
	Symptoms	DoD-001E	Epidemiologic Studies of Morbidity Among Gulf War Veterans: A Search for Etiologic Agents and Risk Factors; Study 5: Seabee Health Study
	Symptoms	DoD-001F	Epidemiologic Studies of Morbidity Among Gulf War Veterans: A Search for Etiologic Agents and Risk Factors; Study 6: A Comparison of Nonfederal Hospitalization Experience Among Veterans in California who have separated from active service: GWV vs. NDV
	Symptoms	DoD-004	The General Well-Being of Gulf War Era Service Personnel from the States of Pennsylvania and Hawaii: A Survey
	Symptoms	DoD-014	Risk Factors Among US Army Soldiers for Enrolling on the Department of Veterans Affairs Gulf War Registry
	Symptoms	DoD-046	Exploratory Data Analysis with the CCEP Database
	Symptoms	DoD-070	War Syndromes from 1900 to the Present: Symptom Patterns and Long-term Health Outcomes

Symptoms and General Health

Epidemiology

Research Focus	Project Focus	Project	Project Title
	Symptoms	DoD-071	A Comparison of Post Deployment Hospitalization Between Vietnam and Gulf War Veterans
	Symptoms	DoD-098	Investigation of a Baseline Medical Database to Evaluate the Health of Military Forces and Veterans
	Prevention	DoD-110	Predictors of Career and Family Dysfunction in Young Adults Enlisting in the United States Navy
	Symptoms	DoD-116B	Patterns of Pre-Persian Gulf War Illness and Health Care Seeking, Pilot Study (See also VA-63B; formerly VA/DoD- 2DB)
	Symptoms	DoD-120	Assessing the Potential Health Impact of the Gulf War on Saudi Arabia National Guard Members and Their Dependents
	Diagnosis	DoD-140	US Department of Defense Surveillance for Neoplasms in Infancy
	Symptoms	DoD-148	Predicting Operational Readiness for Deployed Army National Guard and Army Reserve Soldiers and Families
	Symptoms	DoD-150	Validation Study of Gulf War Deployment Files
	Symptoms	HHS-001	Health Assessment of Persian Gulf War Veterans from Iowa
	Prevention	HHS-009	Improving Health Risk Communications to Prevent Unexplained Illnesses Related to Military Deployments
	Symptoms	HHS-011	Deployment to the Gulf War and the Subsequent Development of Cancer
	Symptoms	VA-002	National Health Survey of Persian Gulf Veterans
	Symptoms	VA-002A	VA National Survey of Persian Gulf Veterans - Phase I
	Symptoms	VA-002B	VA National Survey of Persian Gulf Veterans - Phase II
	Symptoms	VA-004C	Gulf War And Vietnam Veterans Cancer Incidence Surveillance
	Symptoms	VA-046	Diarrhea in Persian Gulf Veterans: An Irritable Bowel-Like Disorder
	Symptoms	VA-063B	Patterns of Pre-Persian Gulf War Illness and Health Care Seeking Pilot Study (See also DoD-116B; previously VA/DoD-
	Symptoms	VA-070	A Clinical Evaluation of the Health Status of Persian Gulf War Veterans in VISN 8

Symptoms and General Health

Epidemiology

Research Focus	Project Focus	Project	Project Title
	Symptoms; Exposure;	DoD-073	Post-deployment Morbid Stress, Behavior and Health: Developing a Model for Predicting Morbidity, Mortality, and other Adverse Outcomes
	Prevention; Symptoms;	DoD-108	Health Status of Current National Guard Members
	Prevention; Symptoms;	DoD-117	Patterns of Pre-Persian Gulf War Illness and Health Care Seeking
	Prevention; Treatment;	HHS-010	Health-e Voice: Optimized Implementation of a Stepped Clinical Risk Communications Guideline
	Symptoms	DoD-015	Comparative Mortality Among US Military Personnel Worldwide During Operations Desert Shield and Desert Storm
	Prevention	DoD-102	Case-Control Study of Fatal Motor Vehicle Crashes Among Gulf War and Non-Deployed Veterans
	Symptoms	VA-001	Mortality Follow-up Study of Persian Gulf Veterans
Brain and Nervous System Function	Symptoms	DoD-039	A Controlled Epidemiological and Clinical Study into the Effect of Gulf War Service on Servicemen and Women of the United Kingdom Armed Forces
Brain and Nervous System Function	Symptoms	DoD-141	Physical, Mental, Social, and Family Health Outcomes of Gulf War Veterans
Brain and Nervous System Function	Symptoms	DoD-142	Illnesses Among Persian Gulf War Veterans: Case Validation Studies (Iowa / Great Britain)
Brain and Nervous System Function	Symptoms	DoD-143	Millennium Cohort Study
Brain and Nervous System Function	Symptoms	DoD-149	Longitudinal Health Study of Gulf War Veterans
Brain and Nervous System Function	Symptoms	VA-002C	VA National Survey of Persian Gulf Veterans - Phase III
Brain and Nervous System Function	Symptoms	VA-005A	Health and Exposure Survey of Persian Gulf Veterans
Brain and Nervous System Function	Symptoms	VA-078	Millennium Cohort Study
Brain and Nervous System Function; Reproductive Health	Symptoms	DoD-045	Air Force Women's Health Surveillance Study
Environmental Toxicology	Symptoms; Exposure;	DoD-074	Relationship of Stress Exposures to Health in Gulf War Veterans

Symptoms and General Health

Epidemiology

Research Focus	Project Focus	Project	Project Title
Environmental Toxicology; Chemical Weapons	Exposure; Symptoms;	DoD-116	VA/DoD Core Funding of the Medical Follow-Up Agency (See also VA-63; formerly VA-DoD-2D/2V)
Environmental Toxicology; Chemical Weapons	Exposure; Symptoms;	VA-063	VA/DoD Core funding of the Medical Follow-Up Agency (See also DoD-116; formerly VA/DoD-2V/2D)
Reproductive Health	Symptoms	DoD-030	Epidemiological Studies Persian Gulf War Illnesses, PG Women's Health Linkage Study
Reproductive Health	Symptoms; Diagnosis; Prevention	DoD-096	Deployment Health Center
Reproductive Health	Symptoms; Prevention;	DoD-001	Naval Health Study Program

Appendix C

Project Funding

(As of September 30, 2004)

NOTES ON REVISED TABLE OF SPENDING FOR GULF WAR VETERANS' ILLNESSES RESEARCH

General Notes

1. All entries for research funding reflect money centrally obligated to researchers (both intramural and extramural) to carry out the specific projects. These funds also cover operational costs for administration, infrastructure, etc. Each department allocates these costs in slightly different ways, making it difficult to completely account for these funds. For example, in VA the research appropriation does not pay for clinician/investigator salaries. By law those funds must come from the patient care appropriation. These salary costs are not included in the obligated costs listed in the table.
2. A "blank" funding entry generally reflects years in which a project was not active (e.g. it had not started or it had come to an end).
3. Some multiyear projects receive all of their funding in the fiscal year of the authorization and appropriation. For those, the dollars authorized and obligated are shown for that fiscal year. The remaining funding entries show $0 for the years that the project is active.
4. Although all projects funded from FY 1994-2004 are listed, only the financial data for FY 1995-2004 (a 10-year window) are shown in Appendix C. Projects that received all of their obligated funds in FY 2004 (or earlier) will, therefore, appear in the table as having no funding.
5. Some intramural projects/programs are supported out of operational costs. For those projects, $0 is entered for the funds in the fiscal years that the project is active.
6. Programs consisting of multiple projects are represented in one of two ways depending on how funds are centrally obligated:
   a**. Funds centrally obligated to the program**: These programs are shown in the table as a main program indicated by project designation such as DoD-1, and projects within the program as DoD-1A, DoD-1B, etc. All funds are shown under the main program. Blank funding entries are shown for the individual projects.
   b. **Funds centrally obligated to projects within a program**: The funds for these programs are only indicated by their projects without a main program identifier, for example, VA-2A and VA-2B.
7. Totals for projects that began prior to 1995 may not reflect the total dollars obligated for their entire funding period.

Specific Notes

1. DoD-4 is part of a larger US Army study conducted at Walter Reed Army Institute of Research. Funding for this project has been combined into project DoD-23. In addition, projects DoD-8A and 8B are part of a larger US Army study in which all funding has been combined and is shown under program DoD-8.
2. HHS-3 was funded from the FY'91 appropriation, which is not included in this accounting.
3. HHS-4 was funded from the FY'93 appropriation, which is not included in this accounting.
4. Funds for VA-1 for FY'94 through FY'97 represent an aggregate of funds for both the VA Mortality Study and the VA National Survey of Persian Gulf Veterans. Beginning in FY'98, VA-1 reflects continuation of the VA Mortality Study. Beginning in FY'98, VA–2A, 2B, and 2C reflect funding for separate components of the VA National Survey of Persian Gulf Veterans.
5. In seven instances (DoD-115 & VA-62, DoD-116 & VA-63, DoD-118 & VA-61, DoD-119 &VA-55, DoD-125 & VA-74, DoD-143 & VA-78 ,and DoD154 & VA-88), two different designations represent the same project because both DoD and VA funded them jointly. The total funding appropriated for each of these five projects is broken down and reported separately by funding agency.

Department of Defense Gulf War Research Funding

PROJECT NO	PROJECT TITLE	STATUS	FY 1995	FY 1996	FY 1997	FY 1998	FY 1999	FY 2000	FY 2001	FY 2002	FY2003	FY 2004	TOTALS* FY '95-'04
DoD-001	Naval Health Study Program	C	$1,010,000	$2,250,000	$2,000,000	$2,654,000							$7,914,000
DoD-001 A	Epidemiologic Studies of Morbidity Among Gulf War Veterans: A Search for Etiologic Agents and Risk Factors; Study 1: A Study of Symptoms among 1500 Seabees.	C											$0
DoD-001 B	Epidemiologic Studies of Morbidity among Gulf War Veterans: A Search for Etiologic Agents and Risk Factors; Study 2: A Comparative Study of Hospitalizations among Active-Duty Personnel Who Participated in the Gulf War and Similar Personnel Who Did Not.	C											$0
DoD-001 C	Epidemiologic Studies of Morbidity among Gulf War Veterans: A Search for Etiologic Agents and Risk Factors; Study 3: A comparative study of pregnancy outcomes among Gulf War veterans and other active-duty personnel.	C											$0
DoD-001 D	Epidemiologic Studies of Morbidity among Gulf War Veterans: A Search for Etiologic Agents and Risk Factors; Study 4: Infertility and Miscarriage in Gulf War Veterans.	C											$0
DoD-001 E	Epidemiologic Studies of Morbidity among Gulf War Veterans: A Search for Etiologic Agents and Risk Factors; Study 5: Seabee Health Study.	C											$0

*Totals for FY 95-04 do not include funds obligated in FY 1992-1994

Status: C=Complete; O=Ongoing

Department of Defense Gulf War Research Funding

PROJECT NO	PROJECT TITLE	STATUS	FY 1995	FY 1996	FY 1997	FY 1998	FY 1999	FY 2000	FY 2001	FY 2002	FY2003	FY 2004	TOTALS* FY '95-'04
DoD-001 F	Epidemiologic Studies of Morbidity among Gulf War Veterans: A Search for Etiologic Agents and Risk Factors; Study 6: A Comparison of Nonfederal Hospitalization Experience Among Veterans in California who have separated from active service: PGW vs. EV.	C											$0
DoD-001 G	Epidemiologic Studies of Morbidity among Gulf War Veterans: A Search for Etiologic Agents and Risk Factors; Study 7: Prevalence of Congenital Anomalies Among Children of Persian Gulf War Veterans.	C											$0
DoD-002	Physiological and Neurobehavioral Effects in Rodents from Exposure to Pyridostigmine, Fuels, and DEET.	C	$0	$0	$0								$0
DoD-004	The General Well-Being of Gulf War Era Service Personnel from the States of Pennsylvania and Hawaii: A Survey.	C											$0
DoD-007 A	Health Risk Assessment of Embedded Depleted Uranium: Behavior, Physiology, Histology, and Biokinetic Modeling.	C											$0
DoD-007 B	Carcinogenicity of Depleted Uranium Fragments.	C					$121,400	$0					$121,400
DoD-008	Program DoD-8.	C	$895,000	$652,000	$695,000	$694,000	$0						$2,936,000
DoD-008 A	Serologic Diagnosis of Viscerotropic Leishmaniasis (VTL).	C	$0	$0									$0
DoD-008 B	Development of a Leishmania Skin Test Antigen (LSTA).	C											$0

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Department of Defense Gulf War Research Funding

PROJECT NO	PROJECT TITLE	STATUS	FY 1995	FY 1996	FY 1997	FY 1998	FY 1999	FY 2000	FY 2001	FY 2002	FY2003	FY 2004	TOTALS* FY '95-'04
DoD-009	Identification of the Genetic Factors Which Control Tropism in Leishmania.	C	$150,000	$0	$0	$0							$150,000
DoD-010	Pyridostigmine Synergistic Toxicity Study.	C	$44,000										$44,000
DoD-011	Male/Female Differential Tolerances to Pyridostigmine Bromide.	C	$359,000	$0	$0	$0							$359,000
DoD-013	Effects of Persian Gulf War Service on Military Working Dogs.	C	$0	$97,000	$200,000	$120,000	$200,000	$0	$0	$0	$0		$617,000
DoD-014	Risk Factors Among US Army Soldiers for Enrolling on the Department of Veterans Affairs Gulf War Registry.	C											$0
DoD-015	Comparative Mortality Among US Military Personnel Worldwide During Operations Desert Shield and Desert Storm.	C											$0
DoD-016	Kuwait Oil Fire Health Risk Assessment.	C	$137,000	$50,000	$127,000								$314,000
DoD-017	Retrospective Studies Involving Military Use of Pyridostigmine as a Pretreatment for Nerve Agent Poisoning.	C											$0
DoD-018	Kuwait Oil Fires Troop Exposure Assessment Model (TEAM).	C	$151,000	$770,000	$193,000	$290,000	$295,000	$295,000	$306,000	$195,000	$225,000		$2,720,000
DoD-019	Persian Gulf Veterans Health Tracking System.	C	$25,000	$0	$0	$450,000	$450,000	$0	$0	$100,000	$50,000		$1,075,000
DoD-021	Study of Variability In Pyridostigmine Inhibition of Blood Cholinesterases in Healthy Adults and Individuals With Symptoms Following Participation in Operation Desert Storm.	C	$100,000	$0	$0								$100,000
DoD-022	Chronic Organophosphorus Exposure and Cognition.	C			$0	$0	$0	$0					$0

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DoD-023	Acute and Long-Term Impact of Deployment to Southwest Asia on the Physical and Mental Health of Soldiers and their Families.	C	$688,000	$764,000	$985,000								$2,437,000
DoD-030	Epidemiological Studies Persian Gulf War Illnesses, PG Women's Health Linkage Study.	C	$779,000	$0	$0	$0	$0	$0	$0				$779,000
DoD-031	Dysregulation of the Stress Response in the Persian Gulf Syndrome.	C	$971,000	$0	$0	$0	$0	$0					$971,000
DoD-032	Neuropsychological Functioning in Persian Gulf Era Veterans.	C	$353,000	$0	$0	$0	$0						$353,000
DoD-033	Effects of Pyridostigmine in Flinders Line Rats Differing in Cholinergic Sensitivity.	C	$354,000	$0	$0	$0	$0						$354,000
DoD-034	Characterization of Emissions from Heaters Burning Leaded Diesel Fuel in Unvented Tents.	C	$283,000	$0	$0	$0	$0						$283,000
DoD-035	Feasibility of Investigating Whether There is a Relationship Between Birth Defects and Service in the Gulf War.	C	$427,000	$10,000	$63,000	$0	$10,500	$0	$0				$510,500
DoD-036	Fatigue in Persian Gulf Syndrome-Physiologic Mechanisms.	C	$416,000	$138,000	$0	$0	$0						$554,000
DoD-037	Neurobehavioral and Immunological Toxicity of Pyridostigmine, Permethrin, and DEET in Male and Female Rats.	C	$934,000	$5,000	$0	$0	$0						$939,000
DoD-038	Diagnostic Antigens of Leishmania tropica.	C	$612,000	$0	$0	$0							$612,000
DoD-039	A Controlled Epidemiological and Clinical Study into the Effect of Gulf War Service on Servicemen and Women of the United Kingdom Armed Forces.	C	$865,000	$0	$28,400	$155,000	$0	$124,868	$0				$1,173,268

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DoD-040	Psychological and Neurobiological Consequences of the Gulf War Experience.	C	$264,000	$0	$0	$0	$0	$0	$0				$264,000
DoD-041	Evaluation of Muscle Function in Persian Gulf Veterans.	C	$906,000	$0	$0	$0	$0	$0					$906,000
DoD-042	The Symptomatic Persian Gulf Veterans Protocol: An Analysis of Risk Factors with an Immunologic and Neuropsychiatric Assessment.	C		$700,000	$0	$0	$0	$0	$0				$700,000
DoD-044	Investigation of Seminal Plasma Hypersensitivity Reactions.	C		$634,000	$0	$5,000	$14,200						$653,200
DoD-045	Physical and Emotional Health of Gulf War Veterans Women.	C		$299,274	$0	$456,732	$20,505	$0	$99,628	$0			$876,139
DoD-046	Exploratory Data Analysis with the CCEP Database.	C		$60,000	$100,000								$160,000
DoD-047	Study of Mycoplasmal Infections in Gulf War Veterans.	C		$112,000	$0	$0							$112,000
DoD-048	Assessment of Genomic Instability via Chromosome 7 Inversion Frequency in a Gulf War Syndrome Cohort vs. Selected Control Groups.	C		$74,000	$0	$0							$74,000
DoD-049	Diagnosis and Dosimetry of Exposure to Sulfur Mustard: Development of Standard Operating Procedures and Exploratory Research on Protein Adducts.	C		$927,000	$0	$0	$0	$0					$927,000
DoD-050	Toxicokinetics of 0-Ethyl S-(2-Diisopropylaminoethyl) Methylphosphonothioate [(+)-VX] in Rats, Hairless Guinea Pigs and Marmosets - Identification of Metabolic Pathways.	C		$699,000	$0	$0	$0						$699,000

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Department of Defense Gulf War Research Funding

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DoD-051	Transgenic Engineering of Cholinesterases: Tools for Exploring Cholinergic Responses.	C		$864,000	$0	$0	$0	$0					$864,000
DoD-052	Female Gender and Other Potential Predictors of Functional Health Status Among Persian Gulf War Veterans.	C											$0
DoD-053	Long-Term Effects of Subclinical Exposures to Sarin.	C		$1,000,000	$400,000	$0	$0	$217,137	$0				$1,617,137
DoD-054	Assessment of Subchronic Neurobehavioral and Neuropathologic Effects in Rats Following Low-Level Sarin Exposure.	C		$315,000	$100,000	$0	$0	$0					$415,000
DoD-055	Low-Level Exposure to GB Vapor in Air: Diagnosis/Dosimetry, Lowest Observable Effect Levels, Performance-Incapacitation, and Possible Delayed Effects.	C		$500,000	$136,000	$0	$0	$0	$0				$636,000
DoD-056	Low-Level Sarin Neurotoxicity and Its Modulation by Pyridostigmine.	C		$685,000	$100,000	$0	$0	$0	$0				$785,000
DoD-057	Physiologic Effects of Stress in Gulf War Veterans.	C			$909,000	$0	$0	$0	$0	$0			$909,000
DoD-058	Illness Among Persian Gulf War Veterans: Case Validation Studies.	C			$2,208,000	$0	$0	$4,264	$267,337	$0	$0		$2,479,601
DoD-059	Pyridostigmine-induced Neurodegeneration: Role of neuronal Apoptosis.	C			$625,000	$0	$0	$0	$0				$625,000
DoD-060	Butyrylcholinesterase Genetic Variants in Persons with Gulf War Illness.	C			$125,000	$0	$0						$125,000

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DoD-061	Neurophysiologic and Neuropathologic Effects in Monkeys of Low Level Exposures to Sarin, Pyridostigmine, Pesticides, and Botulinum Toxoid.	C			$1,586,000	$0	$0	$0					$1,586,000
DoD-062	Sarin and Pyridostigmine Interaction under Physical Stress: Neurotoxic Effects in Mice.	C			$201,000	$0	$0						$201,000
DoD-063	PGW Veterans: Epidemiological and Clinical Evidence for Residual Organophosphate Neurotoxicity.	C			$1,626,000	$0	$0	$0					$1,626,000
DoD-064	Individual Differences in Neurobehavioral Effects of Pyridostigmine.	C			$1,900,000	$18,516	$0	$190,595	$0				$2,109,111
DoD-065	Multi-Disciplinary Pathophysiologic Studies of Neurotoxic Gulf War-Related Neurologic Syndromes Leading to Diagnosis and Treatment.	C			$3,000,000	$0	$0	$0	$0				$3,000,000
DoD-066	Testing for Mycoplasmal Infection Replicability of Nucleoprotein Gene Tracking and Forensic Polymerase Chain Reaction.	C		$49,940	$100,000	$40,000	$403,000	$140,319	$0				$733,259
DoD-067	Antibacterial Treatment Method Based Upon the Excretion of Dead and Decaying Spherical Bacteria.	C			$3,400,000	$0	$0						$3,400,000
DoD-069	Five Year Follow-Up of Army Personnel Potentially Exposed to Chemical Warfare Agents.	O			$946,160	$0	$0	$110,000	$0	$245,910	$0	$0	$1,302,070
DoD-070	War Syndromes from 1900 to the Present: Symptom Patterns and Long Term Health Outcomes.	C			$734,687	$0	$115,000	$0	$0				$849,687

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DoD-071	A Comparison of Post-Deployment Hospitalization Incidence between Vietnam and Gulf War Veterans.	C			$566,000	$0	$0	$0					$566,000
DoD-072	Long-Term Effects of Subchronic Exposure to Sarin, Alone and with Stress and Other Chemicals.	C			$996,000	$0	$0	$0	$0	$0			$996,000
DoD-073	Post-Deployment Morbid Stress, Behavior and Health: Developing a Model for Predicting Morbidity, Mortality, and other Adverse Outcomes.	C			$500,000	$0	$0	$0	$0				$500,000
DoD-074	Relationship of Stress Exposures to Health in Gulf War Veterans.	C			$161,489	$1,991,330	$0	$0	$0	$0			$2,152,819
DoD-075	Toxic Interactions of Prophylactic Drugs and Pesticides.	C				$1,380,157	$0	$0	$0	$0	$0		$1,380,157
DoD-076	Evaluation of Immunotoxicity Due to Concurrent Exposure to DEET, Pyridostigmine, and JP-8 Jet Fuel.	C				$448,369	$0	$0	$0	$0	$0		$448,369
DoD-077	Percutaneous Absorption of Chemical Mixtures Relevant to the Gulf War.	C				$760,031	$0	$0	$0	$0			$760,031
DoD-078	Experimental Models of Gulf War Syndrome.	C				$2,179,097	$444,800	$0	$0	$0			$2,623,897
DoD-079	Time-course of Stress-Induced Impairment of the Blood Brain Barrier.	C			$100,200	$0	$0	$0					$100,200
DoD-080	Molecular Regulation of Corticosteroid Receptor Expression in Stress-Responsive Cells.	C			$297,400	$0	$0	$0	$0	$0			$297,400
DoD-081	Immunotoxicity Due to Coexposure of DEET, Pyridostigmine, and Stress.	C			$300,000	$0	$0	$0	$0	$0			$300,000
DoD-082	Feasibility of Developing a Registry of PTSD-Affected Veteran Sib Pairs.	C			$172,000	$0	$0	$0	$0	$0			$172,000

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DoD-083	Risk for Stress-Related Substance Abuse: Effects of Family History of Alcoholism.	C			$299,700	$0	$0	$0	$0	$0			$299,700
DoD-084	Psychobiological Alterations Of Persian Gulf War Veterans with and without PTSD.	C			$300,000	$0	$0	$0	$0	$0			$300,000
DoD-085	Central Nervous System Cytokines and CRH in Gulf War Veterans with Multiple Unexplained Symptoms.	C			$149,900	$149,200	$0	$0	$0	$0			$299,100
DoD-086	Effects of Combat Stress on the Structure and Function of the Hippocampus.	C			$300,000	$297,800	$0	$0	$0	$0	$0		$597,800
DoD-087	Measurement and Validation of Psychosocial Risk and Resilience Factors Accounting for Physical and Mental Health and Health-Related Quality of Life among PGWVs.	C			$289,100	$0	$0	$0	$68,044	$0	$0		$357,144
DoD-088	Clinical Relevance of Novel Immunological Markers in PTSD.	C			$242,300	$0	$0	$0	$0	$0			$242,300
DoD-089	Limbic Blood Flow and Opiate Receptor PET in Posttraumatic Stress Disorder.	C			$288,500	$0	$0	$0	$0	$0			$288,500
DoD-090	SPECT Benzodiazepine Receptor and MR Imaging in PTSD.	C			$200,000	$100,000	$0	$0	$0	$0			$300,000
DoD-091	Neurological and Circadian Substrates of PTSD-Like Behaviors.	C			$300,000	$299,000	$0	$0	$0				$599,000
DoD-092	Traumatic Experiences Persistently Enhance Cue-dependent Learning: Toward and Animal Model of Chronic Stress and Posttraumatic Stress Disorder.	C			$249,700	$0	$0	$0	$0	$0			$249,700

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DoD-093	Troops Exposed to Nerve Agents at Aberdeen Proving Ground: Follow-Up.	C					$970,700	$0	$0				$970,700
DoD-094	Combined Analysis of the VA and DoD Gulf War Clinical Registries: A Study of Clinical Findings from Systematic Medical Examinations of 100,000 U.S. Gulf War Veterans.	C					$557,173	$206,727	$0	$0			$763,900
DoD-095	Development of Diagnostic tools and alternative treatment drugs for Leishmania.	C					$1,500,000	$1,500,000	$1,500,000	$1,500,000			$6,000,000
DoD-096	Deployment Health Center.	O					$1,500,000	$1,500,000	$2,250,000	$1,750,000	$1,750,000	$1,750,000	$10,500,000
DoD-097	Surveillance of B. pertussis among Military Trainees with Respiratory Disease: Development and Validation of a Highly Sensitive PCR and Beacon Probe based Method for Diagnosis of Pertussis.	C					$177,300	$146,742	$151,202	$151,000			$626,244
DoD-098	Investigation of a Baseline Medical Database to Evaluate the Health of Military Forces and Veterans.	O					$332,500	$188,000	$364,182	$0	$0	$0	$884,682
DoD-099	DoD-wide Medical Surveillance for Potential Long-Term Adverse Events associated with Anthrax Immunization in Active Duty Service Members, Proposal 1: Hospitalizations.	C					$207,876	$204,205	$224,265	$0	$0		$636,346
DoD-100	Antibodies to Squalene.	O					$582,756		$50,000	$487,333	$0	$0	$1,120,089
DoD-101	Mechanisms in Chronic Multisymptom Illnesses.	O					$2,903,408	$5,542,189	$0	$4,786,192	$644,870	$4,527,000	$18,403,659
DoD-102	Case-control Study of Fatal Motor Vehicle Crashes Among Gulf War and Non-deployed Veterans.	C					$249,908	$0	$253,793	$0	$281,950		$785,651

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DoD-103	Human Metabolism & Interactions of Deployment-related Chemicals.	O					$583,319	$46,315	$0	$0	$349,994	$242,424	$1,222,052
DoD-104	Clinical Evaluation of a Proposed New Gulf War Syndrome.	C					$1,003,937	$9,311	$0	$0	$40,844		$1,054,092
DoD-105	Neuroplasticity and Calcium Signaling in Stressed Rat Amygdala.	C					$950,490	$0	$0	$0	$0		$950,490
DoD-106	The role of Th1/Th2 cytokine balance in Gulf War-related Illness.	C					$292,411	$0	$0	$0			$292,411
DoD-107	Stress, Organophosphates and Blood Brain Barrier Integrity.	C					$875,373	$10,825	$0	$0	$0		$886,198
DoD-108	Health Status of Current National Guard Members.	O					$578,970	$0	$264,375	$174,651	$0	$0	$1,017,996
DoD-109	Disordered responses to Orthostatic Stress in the Pathogenesis of Gulf War Syndrome Symptoms.	C					$917,762	$147,523	$397,243	$0	$0		$1,462,528
DoD-110	Predictors of Career and Family Dysfunction in Young Adults Enlisting in the United States Navy.	C					$127,920	$63,705	$0	$0			$191,625
DoD-111	Autonomic Dysfunction in Gulf War Veterans.	O					$999,144	$0	$0	$0	$189,609	$0	$1,188,753
DoD-112	Role of Respirable Saudi Arabian Sand and Pyridostigmine in the Gulf War Syndrome: An Autoimmune Adjuvant Disease?	C					$256,916	$0	$0	$0			$256,916
DoD-113	Interactions of Subsymptomatic Doses of Sarin with Pyridostigmine-Neurochemical, Behavioral, and Physiological Effects.	C					$802,140	$0	$0	$0	$0		$802,140
DoD-114	A Re-Examination of Neuropsychological Functioning in Persian Gulf War Veterans.	C					$593,712	$0	$0	$0			$593,712

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DoD-115	A Randomized Multi-Center Controlled Trial of Multi-Model Therapy in Veterans with Gulf War Illness (EBT) (see also VA-62; formerly VA/DoD-1D).	C					$1,000,000	$2,000,000	$0	$0			$3,000,000
DoD-116	VA/DoD Core Funding of the Medical Follow-up Agency (See also VA-63; formerly VA/DoD-2D).	C	$250,000	$250,000	$250,000	$250,000	$250,000	$250,000	$250,000	$250,000	$250,000		$2,250,000
DoD-116 A	Follow-Up Investigation of Troops Exposed to Nerve Agents at Aberdeen Proving Ground, (Pilot Study) (See also VA-63A; formerly VA/DoD-2DA).	C											$0
DoD-116 B	Patterns of Pre-Persian Gulf War Illness and Health Care Seeking, Pilot Study (See also VA-63B; formerly listed as VA/DoD-2DB).	C											$0
DoD-117	Patterns of Pre-Persian Gulf War Illness and Health Care Seeking.	C						$1,232,050	$0	$0			$1,232,050
DoD-118	An Epidemiological Investigation into the Occurrence of Amyotrophic Lateral Sclerosis (ALS) among GWVs (See also VA-61).	C						$430,824	$832,272	$0			$1,263,096
DoD-119	Antibiotic Treatment of Gulf War Veterans' Illnesses (ABT).(see also VA-055)	C					$500,000	$1,000,000	$0	$0			$1,500,000
DoD-120	Assessing Potential Health Impact of the Gulf War on Saudi Arabia National Guard Members and Their Dependents.	C					$239,000	$316,000	$0	$0			$555,000
DoD-121	Evaluation of the Health Risks of Embedded Depleted Uranium Shrapnel on Pregnancy and Offspring Development.	C			$300,000	$250,000	$25,000	$15,000	$15,000				$605,000

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DoD-122	Carcinogenic Potential of Depleted Uranium and Tungsten Alloys.	C			$25,000	$25,000	$25,000	$30,000	$35,000				$140,000
DoD-123	Immunotoxicity of Depleted Uranium and Heavy Metal Tungsten Alloys.	C					$15,000	$20,000	$15,000				$50,000
DoD-124	Randomized, Controlled Trial of Combination Treatment with Pyridostigmine, DEET, and Permethrin.	C					$1,283,218	$0	$0	$0	$0		$1,283,218
DoD-125	A Randomized Clinical Trial of Cognitive-Behavioral Treatment for PTSD in Women (see also VA-074)	O						$445,078	$0	$0	$0	$0	$445,078
DoD-126	Blood-Brain Barrier Transport of Uranium	O						$790,884	$0	$0	$0	$0	$790,884
DoD-127	Depleted Uranium Fragment Carcinogenicity: Extrapolation of Findings in Rodents to Man	C							$399,582	$0	$0		$399,582
DoD-128	Multifactorial Assessment of Depleted Uranium Neurotoxicity	O						$661,156	$0	$0	$328,734	$0	$989,890
DoD-129	Inhalation of Uranium Oxide Aerosols: CNS Deposition, Neurotoxicity, and Role in Gulf War Illness	O							$1,276,220	$0	$0	$0	$1,276,220
DoD-130	Carcinogenicity and Immunotoxicity of Embedded Depleted Uranium and Heavy-Metal Tungsten Alloys in Rodents	O							$983,164	$0	$0	$0	$983,164
DoD-131	Magnetic Resonance and Spectroscopy of the Human Brain in Gulf War Illness	O							$5,377,526	$0	$500,000	$0	$5,877,526
DoD-132	Impaired Auditory Sensory Gating, Acoustic Startle Response: Effects of Long and Short Deployments on Army Combat Readiness	O							$792,198	$0	$0	$0	$792,198

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DoD-133	Odors, Deployment Stress, and Health: A Conditioning Analysis of Gulf War Syndrome	O							$884,087	$0	$0	$0	$884,087
DoD-134	Identification and Development of Biological Markers of Human Exposure to the Insecticide Permethrin	O						$775,155	$0	$0	$0	$0	$775,155
DoD-135	Biochemical Markers for Exposure to Low Doses of Organophosphorus Insecticides	O						$786,408	$0	$0	$0	$0	$786,408
DoD-136	A Mechanism-Based, Molecular Fingerprint Strategy for Detecting Biomarkers of Organophosphate Exposure	O							$748,858	$0	$0	$0	$748,858
DoD-137	Low Level Exposure to Sulfur Mustard: Development of a SOP for Analysis of Albumin Adducts and of a System for Non-Invasive Diagnosis on Skin	O							$600,111	$0	$0	$0	$600,111
DoD-138	Improving Blood Monitoring of Enzymes as Biomarkers of Risk from Anticholinergic Pesticides and Chemical Warfare Agents	O							$434,795	$0	$0	$0	$434,795
DoD-139	Assessment of the Role of Stress-Activated Kinase in the Pathogenesis of Gulf War Illness	C						$892,399	$500,885	$0			$1,393,284
DoD-140	US Department of Defense Surveillance for Neoplasms in Infancy	O							$764,879	$0	$0	$0	$764,879
DoD-141	Physical, Mental, Social, and Family Health Outcomes of Gulf War Veterans	C							$149,993	$0	$0		$149,993
DoD-142	Illness Among Persian Gulf War Veterans: Case Validation Studies	O									$168,962	$0	$168,962

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Status: C=Complete; O=Ongoing

Department of Defense Gulf War Research Funding

PROJECT NO	PROJECT TITLE	STATUS	FY 1995	FY 1996	FY 1997	FY 1998	FY 1999	FY 2000	FY 2001	FY 2002	FY2003	FY 2004	TOTALS* FY '95-'04
DoD-143	Millennium Cohort Study (see also VA-078)	O						$3,000,000	$1,000,000	$1,250,000	$2,000,000	$1,950,000	$9,200,000
DoD-144	Psychological Health Screening: Methods & Metrics for Deployed Forces	O					$109,000	$295,000	$250,000	$300,000	$0	$0	$954,000
DoD-145	Early Intervention Research Program to Enhance Soldier Resilience	O							$250,000	$275,000	$275,000	$0	$800,000
DoD-146	Assessment of Toxicology Assays Methods & Chemical Exposures Among a Cohort of US Marines Deployed in the Gulf War	C							$100,000				$100,000
DoD-147	Development of Validation of the Automated Neuropsychological Assessment Metric (ANAM) for Deployment Health Monitoring Applications	O			$105,000	$200,000	$190,000	$260,000	$412,000	$696,111	$292,530	$0	$2,155,641
DoD-148	Predicting operational readiness for deployed Army National Guard and Army Reserve soldiers and families	C							$100,000				$100,000
DoD-149	Longitudinal Health Study of Gulf War Veterans	O							$1,689,945	$0	$0	$0	$1,689,945
DoD-150	Validation Study of Gulf War Deployment Files	C								$134,348	$0		$134,348
DoD-151	Mechanisms and Consequences of Vaccine Effects on Th1/Th2 Balance in Gulf War	O								$482,274	$0	$0	$482,274
DoD-152	Characterization of Intracellular Signaling Pathways Activated by Nerve Agents	O								$1,000,000	$1,019,440	$4,500,000	$6,519,440
DoD-153	Gulf War Illness Research	O							$4,694,500	$4,950,000	$920,838	$2,003,000	$12,568,338
DoD-154	Prospective Assessment of Neurocognition in Future Gulf-deployed and Gulf-nondeployed Military Personnel: A Pilot Study (see also VA-088)	O								$100,000	$566,542	$368,687	$1,035,229

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Department of Defense Gulf War Research Funding

PROJECT NO	PROJECT TITLE	STATUS	FY 1995	FY 1996	FY 1997	FY 1998	FY 1999	FY 2000	FY 2001	FY 2002	FY2003	FY 2004	TOTALS* FY '95-'04
DoD-155	Neuropsychological Functioning in Gulf War Veterans Exposed to Pesticides and Pyridostigmine Bromide	O									$1,021,862	$0	$1,021,862
DoD-156	The Effects of Diesel Exhaust and Stress on the Acute Phase Response and Symptoms in the Chemically Intolerant	O									$1,519,951	$0	$1,519,951
	DoD Total Funds		**$10,973,000**	**$11,905,214**	**$28,880,536**	**$13,213,232**	**$22,674,338**	**$23,847,679**	**$28,752,084**	**$18,827,819**	**$12,396,126**	**$15,341,111**	**$186,811,139**

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Department of Health and Human Services Gulf War Research Funding

PROJECT NO	PROJECT TITLE	STATUS	FY 1995	FY 1996	FY 1997	FY 1998	FY 1999	FY 2000	FY 2001	FY 2002	FY2003	FY 2004	TOTALS FY '95-'04
HHS-001	Health Assessment of Persian Gulf War Veterans from Iowa	C	$1,764,762	$1,616,755	$0	$0	$162,000	$0	$0				$3,543,517
HHS-002	Disease Cluster in a Pennsylvania Air National Guard Unit, EPI-AID 95-18	C	$750,000	$0	$0	$16,055	$0	$0					$766,055
HHS-003	Biomarkers of Susceptibility and Polycyclic Aromatic Hydrocarbon (PAH) Exposure in Urine and blood Cell DNA from U.S. Army Soldiers Exposed to Kuwaiti Oil Well Fires	C											$0
HHS-004	Suspected Increase of Birth Defects and Health Problems Among Children Born to Persian Gulf War Veterans In Mississippi	C											$0
HHS-005	Cognitive Function and Symptom Patterns in Persian Gulf Veterans	C				$600,000	$558,000	$660,000	$0	$0	$0		$1,818,000
HHS-006	Defining Gulf War Illness	C				$600,000	$480,000	$719,792	$200,000	$0	$0		$1,999,792
HHS-007	Immunotoxicity of Dermal Permethrin and Cis-Urocanic Acid	C				$175,706	$192,445	$187,647	$0				$555,798
HHS-008	Strategy to Identify Non-Additive Response to Chemical Mixtures	C				$242,586	$247,933	$0	$0				$490,519
HHS-009	Improving Health Risk Communications to Prevent Unexplained Illnesses Related to Military Deployments	O							$337,693	$339,814	$339,814	$0	$1,017,321
HHS-010	Health-e Voice: Optimized Implementation of a Stepped Clinical Risk Communications Guideline	O							$461,177	$460,000	$460,000	$0	$1,381,177
HHS-011	Deployment to the Gulf War and the Subsequent Development of Cancer	O									$164,291	$0	$164,291
HHS-012	Epidemiology of ALS in Veterans	O										$461,951	$461,951
	Total HHS Funds		**$2,514,762**	**$1,616,755**	**$0**	**$1,634,347**	**$1,640,378**	**$1,567,439**	**$998,870**	**$799,814**	**$964,105**	**$461,951**	**$12,198,421**

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Department of Veterans Affairs Gulf War Research Funding

PROJECT NO	PROJECT TITLE	STATUS	FY 1995	FY 1996	FY 1997	FY 1998	FY 1999	FY 2000	FY 2001	FY 2002	FY2003	FY 2004	TOTALS FY '95-'04
VA-001	Mortality Follow-up Study of Persian Gulf Veterans	C	$340,000	$1,980,000	$440,032	$178,197	$166,848	$176,440	$171,154	$128,496			$3,581,167
VA-002	National Health Survey of Persian Gulf Veterans	C											$0
VA-002 A	VA National Survey of Persian Gulf Veterans - Phase I	C				$18,111							$18,111
VA-002 B	VA National Survey of Persian Gulf Veterans - Phase II	C											$0
VA-002 C	VA National Survey of Persian Gulf Veterans - Phase III	C				$1,601,280	$3,571,932	$3,400,000	$2,344,427	$30,000			$10,947,639
VA-003	Use of Roster of Veterans Who Served in Persian Gulf Area	C											$0
VA-004 TOTAL	Boston Environmental Hazards Research Center Program.	C	$500,000	$500,000	$500,000	$500,000	$500,000	$229,500					$2,729,500
VA-004	Boston Environmental Hazards Research Center Program	C											$0
VA-004 A	Evaluation of Cognitive Functioning of Persian Gulf Veterans	C											$0
VA-004 B	Evaluation of Neurological Functioning in Persian Gulf Veterans	C											$0
VA-004 C	Gulf War And Vietnam Veterans Cancer Incidence Surveillance	C											$0
VA-004 D	Evaluation of Respiratory Dysfunction Among Gulf War Veterans	C											$0

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Department of Veterans Affairs Gulf War Research Funding

PROJECT NO	PROJECT TITLE	STATUS	FY 1995	FY 1996	FY 1997	FY 1998	FY 1999	FY 2000	FY 2001	FY 2002	FY2003	FY 2004	TOTALS FY '95-'04
VA-004 E	The Aromatic Hydrocarbon Receptor (AhR) as a Biomarker of Susceptibility	C											$0
VA-004 F	Validity of Computerized Tests	C											$0
VA-005 TOTAL	East Orange Environmental Hazards Research Center Program	C	$500,000	$500,000	$500,000	$500,000	$500,000	$326,900					$2,826,900
VA-005	East Orange Environmental Hazards Research Center Program	C											$0
VA-005 A	Health and Exposure Survey of Persian Gulf Veterans	C											$0
VA-005 B	Physiological and Psychological Assessments of Persian Gulf Veterans	C											$0
VA-005 C	Effects of Exertion and Chemical Stress on Persian Gulf Veterans	C											$0
VA-005 D	Effects of Genetics and Stress on Responses to Environmental Toxins	C											$0
VA-006 TOTAL	Portland Environmental Hazards Research Center: Environment, Veterans' Gulf War Syndrome. Core: Clinical and Epidemiology Research.	C	$499,583	$498,695	$499,198	$499,926	$499,098	$233,290					$2,729,790

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Department of Veterans Affairs Gulf War Research Funding

PROJECT NO	PROJECT TITLE	STATUS	FY 1995	FY 1996	FY 1997	FY 1998	FY 1999	FY 2000	FY 2001	FY 2002	FY2003	FY 2004	TOTALS FY '95-'04
VA-006	Core Program: Portland Environmental Hazards Research Center: Environment, Veterans Health and the Gulf War Syndrome. Core Project for Clinical and Epidemiology Research	C											$0
VA-006 A	Psychosocial, Neuropsychological and Neurobehavioral Assessment (Project I)	C											$0
VA-006 B	Clinical and Neuroendocrine Aspects of Fibromyalgia (Project II)	C											$0
VA-006 C	Neurotoxicity of Environmental Pollutants and Warfare Agents (Project III)	C											$0
VA-006 D	DNA Damage from Chemical Agents and Its Repair (Project IV)	C											$0
VA-006 E	Clinical and Epidemiology Leishmania Research	C											$0
VA-007	Desert Storm Reunion Survey	C	$50,000										$50,000
VA-008	Psychological Test Data of Gulf War Veterans Over Time	C											$0
VA-009	Evaluation of Cognitive Functioning in Persian Gulf War Veterans Reporting War-related Health Problems	C	$20,000										$20,000

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Department of Veterans Affairs Gulf War Research Funding

PROJECT NO	PROJECT TITLE	STATUS	FY 1995	FY 1996	FY 1997	FY 1998	FY 1999	FY 2000	FY 2001	FY 2002	FY2003	FY 2004	TOTALS FY '95-'04
VA-010	Memory and Attention in PTSD	C		$63,700	$57,000	$57,600	$0						$178,300
VA-011	Neuropsychological Functioning in Veterans	C											$0
VA-012	Psychological Assessment of Operation Desert Storm Returnees	C											$0
VA-013	Neurobehavioral Aspects of Persian Gulf Experiences: A Pilot Study	C	$50,000										$50,000
VA-015	Vaccine-Mediated Immunity Against Leishmaniasis	C	$64,300	$0	$82,600	$80,000	$79,400	$41,540	$114,336	$119,600	$59,800		$641,576
VA-016	Protective Immunity in Experimental Visceral Leishmaniasis	C	$60,200	$60,700	$54,900								$175,800
VA-017	Immunological Evaluation of Persian Gulf Veterans	C											$0
VA-018	Chronic Gastrointestinal Illness in Persian Gulf Veterans	C											$0
VA-020	Psychological Adjustment in Operation Desert Shield/Storm Veterans	C											$0
VA-021	A Comparison of PTSD Symptomatology among Three Army Medical Units Involved in ODS	C											$0
VA-036	Stress Symptoms and Their Causal Attribution in Desert Storm Veterans	C											$0
VA-040	Musculoskeletal Symptoms in Gulf War Syndrome	C											$0

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Department of Veterans Affairs Gulf War Research Funding

PROJECT NO	PROJECT TITLE	STATUS	FY 1995	FY 1996	FY 1997	FY 1998	FY 1999	FY 2000	FY 2001	FY 2002	FY2003	FY 2004	TOTALS FY '95-'04
VA-046	Diarrhea in Persian Gulf Veterans: An Irritable Bowel-Like Disorder	C											$0
VA-047	Retrospective Verification of Mustard Gas Exposure	C			$349,700	$299,700	$299,700	$139,960					$1,089,060
VA-048	Cross-Sensitization as a CNS Model for Gulf War Chemical Intolerance	C				$99,900	$89,400	$92,840	$45,000				$327,140
VA-049	Sensitivity to Pyridostigmine Bromide: Persistent Neural Dysfunction	C				$112,090	$147,950	$141,696	$144,024	$125,862			$671,622
VA-050	Neuropsychological findings in a sample of Operation Desert Storm veterans	C											$0
VA-051	Psychobiological Assessment of Desert Storm Veterans	C											$0
VA-053	Spouses and Children Program	C			$101,360	$98,651	$51,088	$33,655	$12,934	$25,000			$322,688
VA-054	Follow-up of Psychological and Neurocognitive Gulf War Outcome: Relation to Stress	O					$53,400	$90,131	$86,895	$86,350	$72,700	$39,375	$428,851
VA-055	Antibiotic Treatment of Gulf War Veterans' Illnesses (ABT) (See also DoD-119)	C					$447,742	$1,466,375	$1,981,963	$254,000			$4,150,080
VA-056	Birmingham's Gulf War Veterans' Illness Demonstration Clinic (13)	C				$54,100	$261,625	$161,175					$476,900

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Department of Veterans Affairs Gulf War Research Funding

PROJECT NO	PROJECT TITLE	STATUS	FY 1995	FY 1996	FY 1997	FY 1998	FY 1999	FY 2000	FY 2001	FY 2002	FY2003	FY 2004	TOTALS FY '95-'04
VA-057	Case Management and Residential Rehabilitation for Persian Gulf War Veterans (13)	C				$71,625	$253,625	$174,750					$500,000
VA-058	Implementation and Evaluation of Gulf War Veterans' Demonstration Project (13)	C				$84,714	$349,805	$262,496					$697,015
VA-059	Demonstration Treatment Program for Gulf War Veterans With Unexplained Physical Symptoms (13)	C				$45,750	$348,225	$259,500					$653,475
VA-060	Identification and Management of Sleep Disorders in Gulf War Veterans	C				$121,125	$328,500	$246,375					$696,000
VA-061	An Epidemiological Investigation into the Occurrence of Amyotrophic Lateral Sclerosis (ALS) Among Gulf War Veterans (See also DoD-118)	C						$0	$0	$110,600			$110,600
VA-062	A Randomized, Multi-Center, Controlled Trial of Multi-Model Therapy in Veterans with Gulf War Illness (EBT) (See also DoD-115; formerly VA/DoD 1V)	C					$788,000	$3,756,826	$1,971,233	$44,250			$6,560,309
VA-063	VA/DoD Core funding of the Medical Follow-Up Agency (See also DoD-116; formerly VA/DoD-2V/2D)	O	$250,000	$250,000	$250,000	$250,000	$250,000	$250,000	$250,000	$250,000	$250,000	$250,000	$2,500,000

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Department of Veterans Affairs Gulf War Research Funding

PROJECT NO	PROJECT TITLE	STATUS	FY 1995	FY 1996	FY 1997	FY 1998	FY 1999	FY 2000	FY 2001	FY 2002	FY2003	FY 2004	TOTALS FY '95-'04
VA-063 A	Follow-Up Investigation of troops exposed to nerve agents at Aberdeen Proving Ground (Pilot Study) (See also DoD-116A; formerly VA/DoD-2VA/2DA)	C											$0
VA-063 B	Patterns of Pre-Persian Gulf War Illness and Health Care Seeking Pilot Study (See also DoD-116B; previously VA/DoD-2VB)	C											$0
VA-064	Boston Environmental Hazards Research Center	O						$112,360	$299,700	$300,000	$297,000	$337,200	$1,346,260
VA-064 A	Functional Neuroimaging in Lead Exposed Adults	O											$0
VA-064 B	Quantification and Validation of Structure-Function relationships through visuospatial test performance	O											$0
VA-064 C	Development of a structured neurotoxicant assessment checklist (SNAC) for clinical use in veteran populations	O											$0
VA-065	San Antonio Environmental Hazards Research Center	O						$116,750	$350,000	$300,000	$300,000	$337,200	$1,403,950
VA-065 A	Does a variant of the human SOD2 gene increase sensitivity to hazards?	O											$0

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Department of Veterans Affairs Gulf War Research Funding

PROJECT NO	PROJECT TITLE	STATUS	FY 1995	FY 1996	FY 1997	FY 1998	FY 1999	FY 2000	FY 2001	FY 2002	FY2003	FY 2004	TOTALS FY '95-'04
VA-065 B	The contribution of FEN-1 to genetic integrity subsequent to oxidative stress	O											$0
VA-065 C	The importance of hydrogen peroxide detoxification in cellular protection	O											$0
VA-065 D	Do defective Gpx1 and ALDH2 genes increase sensitivity to environmental hazards?	O											$0
VA-066	Physiological Responding in Posttraumatic Stress Disorder	C											$0
VA-067	Olfactory Functioning in Gulf War Veterans	C						$7,500	$7,500				$15,000
VA-068	Family Study of Fibromyalgia	C						$46,700	$50,000	$50,000			$146,700
VA-069	Cardiovascular Hyporeactivity and Fatiguing Illness in Gulf War Veterans	C						$122,243	$135,487	$141,815	$48,947		$448,492
VA-070	A Clinical Evaluation of the Health Status of Persian Gulf War Veterans in VISN 8	C				$50,051	$19,817	$6,204	$4,884	$4,900			$85,856
VA-071	Central Nervous System Modulation of Visceral Pain in the Persian Gulf Syndrome	C						$125,313	$181,692	$186,524	$47,975		$541,504
VA-072	Roles of Paraoxonase, Butyrylcholinesterase and Stress in Unexplained Illnesses	C								$50,000	$50,000		$100,000

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Department of Veterans Affairs Gulf War Research Funding

PROJECT NO	PROJECT TITLE	STATUS	FY 1995	FY 1996	FY 1997	FY 1998	FY 1999	FY 2000	FY 2001	FY 2002	FY2003	FY 2004	TOTALS FY '95-'04
VA-073	Pain Sensitivity in Gulf War Veterans with Medically Unexplained Musculoskeletal Pain	C								$50,000	$50,000		$100,000
VA-074	A Randomized Clinical Trial for Cognitive-Behavioral Treatment for PTSD in Women (See DoD-125)	O							$291,804	$896,550	$1,346,863	$1,912,448	$4,447,665
VA-075	ALS and Veterans: Are Veterans at Increased Risk?	O							$73,000	$139,600	$139,600	$78,455	$430,655
VA-076	Analysis of Hippocampal Volume in Aging Combat Veterans with PTSD	O								$145,100	$135,000	$151,740	$431,840
VA-077	HPA Axis Reactivity in Men and Women with Chronic PTSD	O								$101,400	$101,300	$113,861	$316,561
VA-078	Millennium Cohort Study (see also DoD-143)	O											$0
VA-080	Neurochemical and Neurobehavioral Impact of Pyridostigmine Bromide Treatment and Stress	O									$203,400	$119,818	$323,218
VA-081	Stress, Pro-Inflammatory Cytokines and Coping Behavior	O									$193,800	$186,035	$379,835
VA-082	Pituitary Adrenal Function in People with Fatiguing Illness	O								$88,000	$135,000	$151,740	$374,740
VA-083	Neuropsychological Assessment of a Population-Based Sample of Persian Gulf War Veterans and Controls	O								$18,988	$50,000	$31,012	$100,000

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Department of Veterans Affairs Gulf War Research Funding

PROJECT NO	PROJECT TITLE	STATUS	FY 1995	FY 1996	FY 1997	FY 1998	FY 1999	FY 2000	FY 2001	FY 2002	FY2003	FY 2004	TOTALS FY '95-'04
VA-084	Neurobiology of Severe Psychological Trauma in Women	O								$135,000	$135,000	$151,740	$421,740
VA-085	Associative Learning in Veterans with and without Combat Experience	O								$60,400	$74,000	$232,459	$366,859
VA-086	A Clinical Trial of Magnetic Stimulation in Depression	O								$131,400	$131,400	$147,694	$410,494
VA-087	Improving Outcomes of Depression in Primary Care	O								$152,065	$201,926	$218,280	$572,271
VA-088	Prospective Assessment of Neurocognition in Future Gulf-deployed and Gulf-nondeployed Military Personnel: A Pilot Study (see also DoD-154)	O									$24,057	$74,222	$98,279
VA-089	National Registry of Veterans with Amyotrophic Lateral Sclerosis	O									$319,229	$625,564	$944,793
VA-090	Differential Gene Expression in Pathologies Associated with Neuronal Hyperexcitability: Links to Gulf War Illness	O									$250,000	$281,000	$531,000
VA-090A	Neuronal Hyperexcitability and Motor Neuron Regeneration	O											$0
VA-090B	Gene Expression and Proteomic Strategies in Severe Psychiatric Disorders	O											$0

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Department of Veterans Affairs Gulf War Research Funding

PROJECT NO	PROJECT TITLE	STATUS	FY 1995	FY 1996	FY 1997	FY 1998	FY 1999	FY 2000	FY 2001	FY 2002	FY2003	FY 2004	TOTALS FY '95-'04
VA-090C	Developmental Differences in Alcohol Withdrawal Sensitivity	O											$0
VA-090D	Seizures and Neuroplasticity:Physiology and Biochemistry	O											$0
VA-091	The Role of Dietary Choline in Neuroprotection	O										$196,951	$196,951
VA-092	Acetylcholinesterase Activity In Gulf War Veterans	O									$89,920	$49,833	$139,753
VA-093	HPA Axis Alterations in PTSD: A Comparison of Gulf War and Vietnam Veterans	O									$56,750	$36,080	$92,830
VA-094	The Immunology of Chronic Cutaneous Leishmaniasis	O										$192,204	$192,204
VA-095	The Role of Signal Regulatory Proteins in Astrocytomas	O									$54,158	$231,566	$285,724
VA-096	Functional Imaging of Pain in Veterans with Unexplained Muscle Pain	O										$49,035	$49,035
VA-097	Improving a mM-CSF Tumor Vaccine for Established Intracranial Gliomas	O									$99,563	$215,093	$314,656
VA-098	Post-Transcriptional Gene Regulation of VEGF in Malignant Gilomas	O										$44,420	$44,420
VA-099	Vaccination Against Visceral Leishmaniasis with a multi-epitope vaccine	O								$65,700	$123,413	$116,896	$306,009

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Department of Veterans Affairs Gulf War Research Funding

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VA-100	Studies of the Blood-Brain Barrier and its Manipulation	O								$151,875	$151,875	$151,740	$455,490
VA-101	Biomarkers Discovery in ALS	O										$50,518	$50,518
VA-102	Cholinergic and Monoaminergic Influences on Sleep	O							$60,642	$92,588	$92,588	$134,160	$379,977
VA-103	Hypothalamic and Basal Forebrain Regulation of Sleep and Arousal	O									$210,600	$296,657	$507,257
VA-104	Characterization of Pain Processing Mechanisms in the Irritable Bowel Syndrome	O									$114,975	$168,600	$283,575
VA-105	Expression of the Major Surface Protease of Leishmania Chagasi	O								$76,613	$135,628	$298,175	$510,415
	Total VA Funds		**$2,334,083**	**$3,853,095**	**$2,834,790**	**$4,722,820**	**$9,006,155**	**$12,020,519**	**$8,576,675**	**$4,512,676**	**$5,746,467**	**$7,671,771**	**$61,279,051**

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