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Federally Sponsored Research on Gulf War Veterans' Illnesses for 2006

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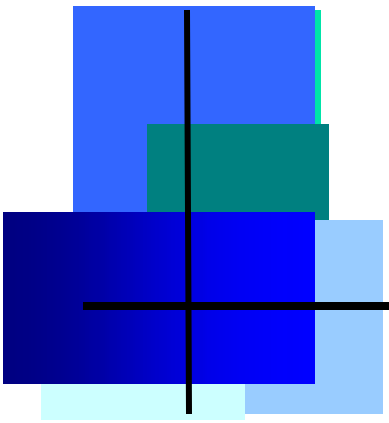
Deployment Health Working Group Research Subcommittee



Annual Report to Congress – 2006

Federally Sponsored Research on Gulf War Veterans' Illnesses for 2005

DEPLOYMENT HEALTH WORKING GROUP
RESEARCH SUBCOMMITTEE MEMBERS

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Carl Hover, LTC, US Army

Department of Health and Human Services:
Drue H. Barrett, PhD, Captain, USPHS
G. Bryan Jones, PhD, Captain, USPHS

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EXECUTIVE SUMMARY

I. INTRODUCTION

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 *2006 Annual Report to Congress*, which is the thirteenth report on Federal research and research activities. The DHWG tracks all federally funded research projects related to Gulf War veterans' illnesses (GWVI).

As in previous *Annual Reports to Congress*, the material presented is divided into 5 sections. Section I is an introduction; Section II summarizes the research priorities and organization of the Federal Gulf War (GW) research portfolio; Section III highlights and summarizes research progress published since the last *Annual Report*; Section IV summarizes Federal funding trends for GW research during the 10-year period from fiscal year (FY) 1997 through FY 2006; and Section V highlights new research projects and initiatives.

II. RESEARCH PRIORITIES

The research priorities remain unchanged from previous years. The 21 Research Topics are grouped into five major Research Focus Areas. These Research Focus Areas are used to organize Sections III and V, as well as Appendix B (Project Listing by Research Focus Area). In November 2005, at the request of the Secretary of Veterans Affairs (VA), the VA Office of Research and Development (ORD) developed a set of criteria for inclusion of VA-funded projects in the GW research portfolio and then evaluated the entire VA research portfolio for projects meeting those criteria. The criteria used as the basis for the review are presented in Section II.

III. RESEARCH RESULTS AND STATUS OF THE FIELD IN 2006

Section III provides brief summaries of research on the health problems of GW veterans which was published in English during calendar year 2006. Research results are grouped according to the five Research Focus Areas used to organize the 21 Research Topics (see Section II): Brain and Nervous System Function, Environmental Toxicology, Immune Function and Infectious Diseases, Reproductive Health, and Symptoms and General Health Status. In this section, published research results are described followed by specific study abstracts taken from PubMed.

IV. RESEARCH FUNDING TRENDS

From FY 1992 through FY 2006 the Departments of Veterans Affairs (VA), Defense (DoD), and Health and Human Services (HHS) funded 330 distinct projects related to health problems affecting GW veterans. 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 GWVI totaled $274.0 million for the period from FY 1997 through FY 2006. As of September 30, 2006, 223 projects (68 percent of the 330 projects) were completed, and 107 projects (34 percent) were new or ongoing.

V. NEW RESEARCH PROJECTS AND INITIATIVES

Ten projects funded through the Congressionally Mandated Medical Research Program (CDMRP) managed by DoD were identified as GW-related. These projects focused on Brain and Nervous System Function (4), Environmental Toxicology (4), and Immune Function and Infectious Diseases (2). Three projects are newly funded in FY 2006 and seven began funding in earlier fiscal years but were not identified in previous *Annual Reports to Congress*.

One project focused on Brain and Nervous System Function was funded by HHS through the National Institute of Environmental Health Sciences. This project was approved for funding in 2004 but was not identified in previous *Annual Reports to Congress.*

VA funded 19 new projects in FY 2006. The primary research foci of these projects included Brain and Nervous System Function (5), Environmental Toxicology (4), Immune Function and Infectious Diseases (2), and Symptoms and General Health (8).

I. INTRODUCTION

The Secretary of Veterans Affairs (VA) 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 GW to the Senate and House Committees on Veterans' Affairs. The Research Subcommittee of the interagency Deployment Health Working Group (DHWG) prepared this *Annual Report to Congress for 2006*, which is the thirteenth report on research and research activities (DHWG, 2004; DHWG, 2005; DHWG, 2006a; DHWG, 2006b; MVHCB, 2001; MVHCB, 2002; PGVCB, 1995; PGVCB, 1996; PGVCB, 1997; PGVCB, 1998; PGVCB, 1999; PGVCB, 2001). The DHWG tracks all federally funded research projects related to GWVI.

As in previous *Annual Reports to Congress*, the material presented is divided into five sections. Section I is an introduction. Section II summarizes the research priorities and organization of the Federal GW research portfolio. Section III highlights and summarizes published research progress since the last *Annual Report*. Section IV summarizes Federal funding trends for GW research during the 10-year period from FY 1997 through FY 2006. Section V highlights new research projects and initiatives since the last *Annual Report*.

II. RESEARCH PRIORITIES

A. Twenty-One Research Topics

VA, DoD, and HHS created the Persian Gulf Veterans Coordinating Board (PGVCB) to coordinate research on GWVI. 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 two additional questions in 1996. (PGVCB, 1996b) The comprehensive GW research portfolio has addressed each of these 21 questions, and relevant results have been published on each one. The Military 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). The Research Subcommittee of the DHWG, which was established to address a broader range of deployment health issues, reviewed the 21 questions and replaced them with a corresponding list of 21 Research Topics for the *Annual Report to Congress for 2004* (DHWG, 2006a). The organization of the Research Topics into five major categories is presented below.

The Institute of Medicine of the National Academies (IOM) review of the scientific literature on infectious diseases indicates that very few cases of Leishmaniasis have been reported that can be linked to military service during the GW (Institute of Medicine, 2006b). In addition, there have been few, if any, reports on other infectious diseases that have proven to be relevant to the long-term symptoms of ill GW veterans. Based on this review of the scientific literature, there is no rationale to continue inclusion of infectious diseases as an area of research that will provide answers to the causes or cure for these symptoms. In terms of the original 21 questions described below, this means the removal of questions 2 and 19 and the refocusing of the third Research Focus Area from Immune Function and Infectious Diseases to just Immune Function. These changes will be reflected in next year's Annual Report to Congress; projects directed at these questions will continue to be listed in Appendices A and B but no new funding amounts will be shown for FY 2007.

The IOM report reviewing the available literature on Amyotrophic Lateral Sclerosis (ALS) in veterans (Institute of Medicine, 2006a) concluded there is limited and suggestive evidence of an association between military service and later development of ALS. This strengthens the decision to include ALS as a relevant topic in the 2005 Portfolio review described on pages 6-7. ALS projects included in the GW portfolio are primarily focused on epidemiologic studies in GW veterans and the development of new methodologies to identify and/or treat ALS.

Brain and 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 or weapons bunker at Khamisiyah (Question 5)
- Chemical agents, other than at Khamisiyah (Question 6)
- Pyridostigmine bromide and other medical prophylaxes (e.g. vaccines and anti-malarials) (Question 7)
- Psychophysiological stressors (Question 8)
- Short term, low level exposures to pyridostigmine bromide, DEET, or permethrin, alone or in combination as a cause of 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

- Increased prevalence or severity of symptoms and/or illnesses (Question 1)
- Nonspecific symptoms and symptom complexes (e.g., chronic multisymptom illnesses) (Question 9)
- Changes in lung function or airway reactivity (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. Research Portfolio Descriptors

VA maintains a research database of federally sponsored research on GWVI. 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 Research Subcommittee of the DHWG attempts to stay abreast of all research relevant to GWVI. This is accomplished by monitoring peer-reviewed published scientific literature, attending scientific meetings, and even using newspaper reports and personal accounts of researchers.

Appendix A lists the projects that VA, DoD, and HHS have funded to date. Research projects are grouped according to the department that is responsible for funding. Dual-funded projects are listed under both departments.

Appendix B lists all federally funded GW 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 Area** of the project. The five Research Focus Areas are also used to organize the 21 Research Topics (see Section A, above).

- Brain and Nervous System Function (e.g., studies on neurological or psychological deficits and/or alterations)
- Environmental Toxicology (e.g., studies focused on specific environmental exposures such as pesticides, oil well fires, jet fuel, vaccines, medical prophylactic agents, etc.)
- Immune Function and Infectious Diseases (e.g. studies on alterations in immune function, host defenses, or detection and treatment of infectious diseases)
- Reproductive Health (e.g. studies on sexual and/or reproductive dysfunction)
- Symptoms and General Health (e.g., studies on mortality, pulmonary disease, cancer, chronic multisymptom illnesses, etc.)

Secondary and/or tertiary Research Focus Areas from the above list may also be assigned. Two additional Research 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 and other medical prophylaxes (e.g., vaccines, pyridostigmine bromide, antimalarials, etc)

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

- Diagnosis: studies that will improve the ability to diagnose previously unexplained conditions, or to better refine diagnoses with new tools
- Exposure: studies that examine individual exposures and/or interactions of exposures (chemical, biological, pharmacological, physiological, etc.)
- Interactions: interactions of combined exposures (chemical, biological, pharmacological, physiological, etc.)
- Prevention: studies that will produce knowledge that could lead to disease prevention strategies
- Symptoms: 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**. Each research project on GWVI uses a method of approach to test a specific research hypothesis. 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 into underlying mechanisms of diseases and illnesses using in vitro and in vivo models.

CLINICAL: 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: 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 tracking research on GWVI, the 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 GWVI, 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 GWVI catalogs only research and development activities that either directly involve GW veterans or 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 more generalized biomedical research over the past 50 years.

C. Portfolio Criteria

In November 2005, at the request of the Secretary of VA, the VA Office of Research and Development (ORD) developed a set of criteria for inclusion of VA-funded projects in the GW research portfolio. The criteria and relevant references are presented below. These criteria are now routinely used to identify relevant research projects. New projects selected for funding must meet these criteria and are presented in Section V.

1. Studies of chronic multisymptom illnesses (CMI) affecting GW veterans, including case definitions for CMI in GW veterans and the general population.
   a) Case definitions of multisymptom illnesses affecting GW veterans
      (Fukuda et al., 1998; Haley et al., 1997a; Haley et al., 1997b; Haley et al., 2002; Wolfe et al., 2002)
   b) Chronic fatigue syndrome
      (Dunphy et al., 2003; Eisen et al., 2005; Gray et al., 2002; The Iowa Persian Gulf Study Group, 1997; Unwin et al., 1999)
   c) Fibromyalgia
      (Eisen et al., 2005; The Iowa Persian Gulf Study Group, 1997)
   d) Irritable bowel syndrome
      (Dunphy et al., 2003; Gray et al., 1999)
   e) Multiple chemical sensitivity
      (Fiedler et al., 2004; Gray et al., 2002)
1. Conditions and/or symptoms occurring with higher prevalence in GW veterans
   a) Fatigue
      (CDC, 1995; Coker et al., 1999; Doebbeling et al., 2000; Fukuda et al., 1998; Gray et al., 1999; Haley et al., 1997b; The Iowa Persian Gulf Study Group, 1997; Unwin et al., 1999; Wolfe et al., 2002)
   b) Joint and muscle pain
      (CDC, 1995; Coker et al., 1999; Fukuda et al., 1998; Gray et al., 1999; Haley et al., 1997a; Haley et al., 1997b; Haley et al., 2002; Kang et al., 2000; Pierce, 1997; Proctor et al., 1998; The Iowa Persian Gulf Study Group, 1997; Wolfe et al., 2002)
   c) Gastrointestinal complaints (dyspepsia, gastritis, diarrhea, etc.)
      (Blanchard et al., 2006; CDC, 1995; Coker et al., 1999; Eisen et al., 2005; Fukuda et al., 1998; Gray et al., 1999; Haley et al., 1997b; Kang et al., 2000; Proctor et al., 1998)
   d) Cognitive dysfunction (memory, attention, etc.)
      (CDC, 1995; Coker et al., 1999; Fukuda et al., 1998; Gray et al., 1999; Haley et al., 1997b; Kang et al., 2000; Knoke et al., 2000; Proctor et al., 1998; The Iowa Persian Gulf Study Group, 1997; Wolfe et al., 2002)
   e) Sleep disturbances
      (CDC, 1995; Coker et al., 1999; Gray et al., 1999; Haley et al., 1997b; Kang et al., 2000; Knoke et al., 2000; Pierce, 1997; Proctor et al., 1998; Unwin et al., 1999; Wolfe et al., 2002)
   f) Central Nervous System disorders (ALS, glioblastoma, imaging studies, etc.)
      (Bullman et al., 2005; Haley, 2003; Horner et al., 2003; Weisskopf et al., 2005)
   g) Headaches
      (CDC, 1995; Coker et al., 1999; Fukuda et al., 1998; Gray et al., 1999; Haley et al., 1997b; Kang et al., 2000; Knoke et al., 2000; Proctor et al., 1998; Unwin et al., 1999; Wolfe et al., 2002)
   h) Dermatologic conditions
      (CDC, 1995; Coker et al., 1999; Eisen et al., 2005; Fukuda et al., 1998; Gray et al., 1999; Kang et al., 2000; Knoke et al., 2000; Pierce, 1997; Proctor et al., 1998; Wolfe et al., 2002)

2. Long-term health effects of potentially hazardous substances, alone and in combination, to which GW veterans may have been exposed to during deployment.
    a) Pyridostigmine bromide
    b) DEET
    c) Permethrin
    d) Oil well fire smoke
    e) Petroleum products (e.g., jet fuels) and combustion products
    f) Multiple vaccinations and other medical prophylaxes

a. Other topics from the 21 Topics forming the framework for the *Annual Report to Congress on Federally Sponsored Research on GW Veterans' Illnesses:*
    a) Altered immune function and/or host defense
    b) Exposure to, and prevalence of, leishmania tropica
    c) Physiological responses to biological stress
    d) Sexual and/or reproductive dysfunction

III. RESEARCH RESULTS AND STATUS OF THE FIELD IN 2006

In 2006, numerous research studies provided new and detailed information on the health problems of GW veterans. A PubMed search retrieved 122 relevant articles published in English in calendar year 2006. These articles include federally and non-federally funded research, as well as international research. This section provides brief highlights of published research in calendar year 2006, followed by the PubMed abstracts. Where possible the project number from the GW database or the source of funding for the described research is included with each abstract.

This report presents published research based on the five Research Focus Areas used to organize the 21 Research Topics: Brain and Nervous System Function; Environmental Toxicology; Immune Function and Infectious Diseases; Reproductive Health; and Symptoms and General Health Status.

A. Brain and Nervous System Function

In 2006, 24 reports were published with a primary emphasis on research relevant to understanding the brain and nervous system functioning in GW veterans. One review of neuropsychological and neuroimaging research reported no evidence of a non-specific effect of GW service related to brain structure changes or function, and proposed directing efforts towards clinical management over a focus on further attempts to define etiology (Vasterling and Bremner, 2006). Another review examined stressors and their effects on soldiers who deployed to Operation Desert Shield (Gifford et al., 2006).

A 10-year retrospective study suggested that psychiatric morbidity was related to greater separation from the military in an Australian Navy cohort over 1991-2001 (Creamer et al., 2006). Further, a study of psychiatric symptoms among GW veterans showed a higher prevalence of anxiety and depression compared to non-Gulf deployed veterans (Fiedler et al., 2006). In a comparison between distinguishing factors of personality and mood and anxiety disorders, Gamez et al. reported depression, generalized anxiety disorder and post-traumatic stress disorder (PTSD) were related to personality more than other anxiety disorders (Gamez et al., 2006). In a study of GW veterans refugees in the United States, PTSD scores and health outcomes were associated, as well as higher rates of health care utilization (Jamil et al., 2006). Black and co-workers found that 43 percent of GW veterans showed one or more Borderline Personality Disorder (BPD) traits. These traits were associated with significant psychiatric morbidity and increased service use, and findings suggest that BPD symptoms need to be considered in treating GW veterans (Black et al., 2006). Arguelles et al. reported an association in twins between the symptoms of Post Traumatic Stress Disorder (PTSD) measured on the Impact of Events Scale and chronic widespread pain; however the association did not appear to be explained by genetics as the differences between monozygotic and dizygotic twins were not significant (Arguelles et al., 2006).

A series of imaging work related to GW VI was also published during 2006. Woodward and co-workers reported that hippocampal volume was decreased in subjects with a history of alcoholism and PTSD compared to nonalcoholic subjects with PTSD (Woodward et al., 2006a). In a second study, they found lower anterior cingulate cortex volume in veterans with combat-related PTSD compared to those who did not have PTSD (Woodward et al., 2006b). Yehuda and co-workers found no hippocampal volume differences between veterans with PTSD and those without, but veterans with PTSD showed poorer memory performance and lower urinary cortisol levels (Yehuda et al., 2006c). Spence and co-workers proposed an alternative method to detect changes in regional blood flow using single photon emission computed tomography (SPECT), which may be more sensitive in GW veterans' brain regions with lower SPECT emissions, such as the insula and frontal cortex (Spence et al., 2006).

Several small PTSD treatment trials showed some initial beneficial effects. A study of a small number of veterans suggested an initial beneficial effect of citalopram for combat-related PTSD over four weeks; however that effect was not sustained by the eighth week of treatment (English et al., 2006). Cognitive behavioral therapy was reported beneficial in a small trial comparing Cognitive Processing Therapy vs. waitlist control (Monson et al., 2006). Maher and co-workers considered the findings to date on sleep disturbances related to PTSD and reported that sleep disordered breathing and sleep movement disorders are more common in patients with PTSD. Further, evidence reviewed suggested many medications may help alleviate PTSD related sleep disturbances including some selective serotonin reuptake inhibitors and prazosin, while benzodiazepines, tricyclic antidepressants and monoamine oxidase inhibitors are not effective (Maher et al., 2006).

Several papers on neuroendocrine alterations in PTSD were published. The first describes the current status of understanding neuroendocrine alterations in PTSD (Yehuda, 2006). The second presents an experimental study which found higher levels of plasma neuropeptide Y (NPY) in combat-exposed veterans without PTSD, suggesting a possible protective role for NPY for PTSD (Yehuda et al., 2006a). Furthermore, greater PTSD symptom improvement was related to dehydroepiandrosterone-sulfate levels as well as a lower cortisol/dehydroepi-androsterone ratio in the PTSD group (Yehuda et al., 2006b). In another series of studies, GW veterans showed a significant effect of deployment, but not PTSD on neuroendocrine changes; Adrenocorticotropic hormone levels were lower in deployed GW veterans compared to non-deployed (Golier et al., 2006a) and cortisol suppression was associated with musculoskeletal problems in veterans who took anti-nerve gas pills (Golier et al., 2006b)

Several reports concerning GW veterans and ALS were published in 2006. A review by Rose and Brix suggests that while no differences were found across studies for neurological function and rates of neurological abnormalities in GW veterans and controls, ALS incidence appeared to be elevated in US GW veterans (Rose and Brix, 2006). Potential cerebrospinal fluid biomarkers for ALS that could be used diagnostically were identified by Pasinetti and coworkers; a three protein panel identified 95% of ALS patients compared to normal controls and disease controls (Pasinetti et al., 2006). The theory that environmental exposures might be a risk factor for ALS was examined by studying the association between genetic polymorphisms for sporadic ALS and paraoxonases (PONs) that work to detoxify pesticides and chemical nerve agents. Two studies reported significant associations with PONs variants and sporadic ALS (Saeed et al., 2006; Slowik et al., 2006).

B. Environmental Toxicology

In 2006 there were numerous reports on potentially toxic environmental agents that GW veterans may have been exposed to in theater. These toxic agents fall in four broad groups: (1) depleted uranium (DU), which is used in armor-piecing munitions, (2) organophosphate based nerve agents (e.g., sarin) and prophylactic protective agents (e.g., pyridostigmine bromide), (3) insecticides (e.g., permethrin) and insect repellents (e.g., DEET), and (4) exposure to organic solvents (e.g., jet fuel).

Glass and colleagues described the results of a postal questionnaire to Australian veterans involving self-reported chemical and environmental exposures specifically associated with either their 1991 GW deployment or to other active deployments. Six of 28 investigated exposures were experienced more frequently during the GW than during other deployments; these were exposure to smoke, exposure to dust, exposure to chemical warfare agents, use of respiratory protective equipment, use of nuclear, chemical, and biological protective suits, and entering/inspecting enemy equipment (Glass et al., 2006). In a second report, these authors commented that while exposure assessment is difficult to do well in studies of any workplace environment, it is made more difficult in GW studies where there

are a number and variety of possible exposures, no agreed metrics for individual exposures and few contemporary records associating the exposure with an individual (Glass and Sim, 2006). There were several reports in 2006 regarding studies of humans exposed to DU. Although GW veterans who were wounded by DU-munitions and who still have DU fragments in their bodies continue to have elevated urinary uranium even after 12 years, there have been no observed kidney or other clinical abnormalities (McDiarmid et al., 2006; Squibb and McDiarmid, 2006). Ough and co-workers reported on a study to compare the inter-laboratory reliability of measuring DU levels in urine samples at 5 different laboratories (Ough et al., 2006). Danish soldiers exposed to DU during deployment to the Balkans from 1992 to 2001 showed no increased risk for leukemia or testicular cancer (Storm et al., 2006). Quantifying human exposure to DU, particularly when exposure occurred months to years before, was shown to be possible with a sensitive test to measure isotopic composition in urine; the test was shown to be sensitive, precise and reproducible between laboratories (Parrish et al., 2006).

The effects of DU exposure have been directly tested in several animal studies. DU inhibited glucose uptake in the rat kidney (Goldman et al., 2006) and intramuscular injection of DU produced a short-term (3-7 days), dose-dependent decrease in kidney function (Fukuda et al., 2006). Oral administration of DU altered the activity and expression of enzymes in the liver and kidney involved in vitamin D metabolism (Gueguen et al., 2006; Tissandie et al., 2006), altered plasma concentrations of the active form vitamin D, and altered tissue expression of vitamin D receptor (Tissandie et al., 2007).

Muse and colleagues reported on a new method to measure low levels of sarin in air samples from animal studies of sarin toxicity (Muse et al., 2006). DU is concentrated in a tissue-specific manner, and varies with acute vs chronic exposure (Monleau et al., 2006a; Paquet et al., 2006). The brains of DU implanted rats concentrate uranium in a region-specific manner (Fitsanakis et al., 2006); based on a variety of biomarkers, however, toxic effects were not detected (Dobson et al., 2006). Ingested DU had no toxic effect on immune status or function of the rat intestine, even though uranium was concentrated in both areas (Dublineau et al., 2006a; Dublineau et al., 2006b; Paquet et al., 2006). Exposure of isolated liver cells to DU, however, produced toxic effects that appeared to involve reduced levels of biological metabolites and increased production of free radicals (Pourahmad et al., 2006). Rats that inhaled DU showed increased DNA strand breaks, increased inflammatory cytokine expression and increased hydroperoxides in the lung (Monleau et al., 2006c; Monleau et al., 2006b).

Isolated murine peritoneal macrophages and CD4+ cells exposed to DU showed a dose-dependent cytotoxicity and altered gene expression, particularly involving genes related to signal transduction (Wan et al., 2006). Isolated hamster ovary cells also showed altered gene expression after exposure to DU (Coryell and Stearns, 2006).

In GW veterans exposed to variable amounts of organophosphates (i.e., sarin and cyclosarin) during the destruction of the munitions dump at Khamisiyah, Iraq there was an association between exposure and reduced neurobehavioral functioning on tasks of fine psychomotor dexterity and visuospatial abilities, even four to five years after exposure (Proctor et al., 2006).

Rats exposed to sarin showed significant alterations in gene expression in degenerative and regenerative pathways in their brains that may contribute to observed neurodegeneration and subsequent neuropathological alterations. These effects were moderated by sarin dose, duration of exposure, and age of the animals (Damodaran et al., 2006a; Damodaran et al., 2006b). Exposure of rats to levels of cyclosarin that produced convulsions and other severe clinical signs of toxicity also produced performance deficits on learned behavior that did not appear to persist (Genovese et al., 2006a). Conversely, rhesus and African green monkeys exposed to low levels of sarin showed no changes in measures of behavioral performance (Genovese et al., 2006b). Guinea pigs repeatedly exposed to low doses of sarin showed alterations in EEG patterns and reduced choline levels in specific brain areas, but no measurable effects on brain or heart pathology (Shih et al., 2006a). When rats were exposed to repeated low doses of sarin, delayed or persistent alterations in brain cholinergic function were not observed (Shih et al., 2006b). Mice exposed to low doses of sarin showed altered autonomic function (i.e., heart rate) although the dose used produced no measurable peripheral cholinergic effects (Morris et al., 2007).

Several studies addressed the effects of different treatments for sarin exposure. Pyridostigmine bromide (PB), a neuroprotective agent, also inhibits acetylcholinesterase activity and therefore has toxicity (Maxwell et al., 2006). Subjects given the approved dose of PB did not exhibit short-term physical or neurocognitive impairment (Roy et al., 2006a). PB was shown to have enhanced toxicity in rats when the animals experienced combined multiple

stressors; this enhanced toxicity was not associated with increased cholinesterase inhibition in either central or peripheral tissues (Baireddy et al., 2006). Rats given repeated low doses of sarin and PB did not demonstrate persistent or delayed alterations in autonomic function (e.g., heart rate) or in locomotor activity (Scremin et al., 2006). Rats given low does of pyridostigmine, sarin or a combination showed no alteration in cholinergic function. The timing of treatment of rats with an anticonvulsive (i.e., midazolam) after exposure to sarin was critical in modulating neuroinflammatory responses (Chapman et al., 2006b).

Exposure to various insecticides (e.g. permethrin) and insect repellent (e.g. DEET) was common during the GW. A new, more specific and sensitive indirect enzyme-linked immunosorbent assay for the breakdown product of permethrin in human urine was recently developed (Ahn et al., 2006). Cherstnakova and colleagues used a different method for measuring DEET, permethrin, and PB in human plasma to determine the pharmokinetics/pharmacodynamics of combined exposure of DEET placed on the skin, permethrin on treated uniforms and oral doses of PB (Cherstniakova et al., 2006). Although permethrin was not detected in the blood when it was applied to clothing, DEET applied directly on the skin could be detected in the blood (Roy et al., 2006a; Vijayalaxmi et al., 2006). El-Masry and Abou-Donia examined the interaction of PB and DEET to explain the increased toxicity and bioavailability of PB following combined administration of the two compounds (El-Masry and Abou-Donia, 2006). Combined and correct use of PB, DEET and permethrin was well-tolerated in humans and there was no evidence of short-term physical or neurocognitive impairment (Roy et al., 2006b). Isolated mouse cells treated with pesticides such as permethrin generated increased amounts of superoxide radicals and hydrogen peroxide, compounds with known toxic effects (Olgun and Misra, 2006).

Several studies reported on the effects of jet fuel exposure on isolated human cells. Exposing human skin cells to JP-8 jet fuel for one minute altered the expression of over 151 genes (Chou et al., 2006). Different components of jet fuel had different toxic effects on human skin cells (Yang et al., 2006). Exposing mice to JP-8 or JETA did not have an effect on bone marrow cells or in cells from peripheral blood, regardless of different types of exposure (Vijayalaxmi et al., 2006).

C. Immune Dysfunction and Infectious Diseases

Peakman and co-workers examined the available epidemiological evidence and concluded that a single vaccination is not likely to be a significant cause of chronic fatigue syndrome-like illnesses. They found a modest relationship with multiple vaccinations, but this relationship may be affected by recall bias. The studies available at this time do not identify any immunological basis for such a GW-related illness (Peakman et al., 2006).

In a study of GW veterans, Allen and co-workers found that long-lasting immune responses are generated with vaccines against anthrax and plague. Antigen-specific T cell responses are present 12 to 15 years after vaccination, and these responses are as great as those seen with tetanus-diphtheria vaccination (Allen et al., 2006).

A series of animal studies was designed to investigate whether administration of a combination of vaccines and PB, a pretreatment against possible nerve agent poisoning, could result in illness in GW veterans. The addition of PB had no effect on immune responses to the vaccines (Griffiths et al., 2006). Urinary cortisol was measured in the animals as an index of physiological stress; combined treatment with vaccines and PB had no effect (Hornby et al., 2006). Brain electrical activity and sleep were observed, and there were no changes in electroencephalograms (EEG) or sleep patterns that could be attributed to the combined treatment (Williams et al., 2006). Researchers measured cognitive behavior, muscle function, and general health in the treated animals, and there were no marked long-term changes observed (Stevens et al., 2006).

Del Giudice and co-workers demonstrated that antibodies to squalene, were detectable in the serum of subjects who were never immunized with vaccines containing squalene. They also showed that vaccination with influenza vaccine containing squalene adjuvant (MF59C; marketed in Western European countries) did not induce anti-squalene antibodies, and did not increase the amount of such antibodies in subjects who already had them (Del Giudice et al., 2006). Spanggord and co-workers developed and validated a highly sensitive method of analysis for squalene using high-performance liquid chromatography, and tested 44 bottles of 38 lots of anthrax vaccine for the presence of the chemical. In 43 bottles of 37 lots, no squalene was detected (Spanggord et al., 2006)

There is risk of transmission of visceral leishmaniasis in the Middle East through bites from sand flies. Disease progression may be predicted by testing immune function in patients, but most clinical studies of patients with leishmaniasis have used methods that require a large sample of blood. Kurkjian and colleagues have developed a multiplexed microsphere assay (MMA) to test immune function in leishmaniasis that requires less time and a smaller blood sample (Kurkjian et al., 2006).

D. Reproductive Health

Three studies on reproductive health related to GW research were published in 2006. None of the studies found an adverse impact of GW-related service on reproduction. A review of the scientific literature indicated that for male veterans who served in the first GW there was no effect on risk of birth defects or stillbirth in children born after deployment (Doyle et al., 2006). Male and female GW veterans and veterans who were not deployed showed similar numbers of reported pregnancies. There were no differences in birth weights of infants born to the two groups, and the risk for ectopic pregnancies, stillbirths, and miscarriages were similar (Wells et al., 2006). An animal study showed no adverse effects from implanted DU pellets on male reproductive function (Arfsten et al., 2006).

E. Symptoms and General Health

Several studies examined the persistence of symptoms in GW veterans. Ozakinci and co-workers conducted a five-year follow-up survey of members of the U.S. Department of Veterans Affairs GW Registry who were previously evaluated in 1995 and 2000; no significant changes in the number of symptoms or their severity over the last five years were found (Ozakinci et al., 2006). Blanchard and co-workers found that, ten years after the GW, chronic multi-symptom illness was still more prevalent among deployed veterans than among nondeployed veterans (Blanchard et al., 2006). A systematic review of 23 papers published between January 1990 and May 2004 that compared the prevalence of chronic fatigue syndrome (CFS), multiple chemical sensitivity, CDC-defined chronic multi-symptom illness, fibromyalgia, or symptoms of either fatigue or numbness and tingling in GW veterans and non-GW veterans found that veterans deployed to the GW were more likely than non-GW veterans to report multi-symptom conditions, including CFS (Thomas et al., 2006b). A study of random sample of UK Armed Forces (Murphy et al., 2006) found that there were differences in health outcomes between GW and non-GW groups for symptomatic measures, but not psychological (such as PTSD) or behavioral measures (such as alcohol consumption). Australia undertook a study of Australian veterans of the GW, who were mostly naval. Sim and Kelsall reported that no unique symptom clusters were identified; however, several psychological disorders occurred in excess in the Australian GW group that were associated with GW psychological stressors (Sim and Kelsall, 2006). A study of Royal Australian Navy veterans of the GW used a self-report instrument to determine if any subgroups were at higher risk of harmful alcohol use. The highest risk subgroup was current smokers, followed by former or never smokers who were either not married or married with a diagnosis of major depression (McKenzie et al., 2006).

Eisen and co-workers concluded that ten years after the GW, the general physical health of spouses of GW deployed veterans was similar to that of spouses of nondeployed veterans (Eisen et al., 2006).

Kang and colleagues published the results of three studies on health concerns of GW veterans. The first study reported on the exposures, clinical status, and health care use of 53 veterans (79% served in the GW) who participated in the VA National Referral Program from January 2002 until March 2004. Diagnoses included CFS, neurotic depression, and PTSD. The results suggest that the program may help veterans with long and complex medical problems (Lincoln et al., 2006a). A second study examined the medical records of registrants in the VA and DoD GW-related illness registries and found that subjects had significantly more pre-deployment outpatient visits than controls. Although the number of certain types of outpatient visits was associated with post-deployment multi-symptom illness, these associations had limited predictive value (Miller et al., 2006). The third study examined published studies about health care use and mortality among GW veterans. The authors concluded that with a few exceptions, such as ALS, mental disorders, and cancer, it is time to stop examining GW veteran morbidity (Gray and Kang, 2006).

Previous studies have shown that veterans with GWVI benefit from regular exercise. In a VA Cooperative Study, ill GW veterans were treated with exercise alone or exercise combined with cognitive-behavioral therapy. Compliance was less than 50% during the treatment phase and was predicted by less pain and greater age, motivation, and body mass index (Mori et al., 2006).

Salamon and co-workers studied over 5,000 French GW veterans by means of a self-administered mail questionnaire and a standardized clinical evaluation. The most frequent symptoms were headaches, neurological or psychological symptoms, and back pain. Respiratory, neurocognitive, and musculoskeletal symptoms similar to those reported from other studies of ill GW veterans were also observed, but no other clusters were identified (Salamon et al., 2006). Smith and co-workers examined the hospitalization records for all active duty personnel deployed exclusively to the GW, Southwest Asia after the GW, or Bosnia. Compared to GW veterans, personnel deployed to Southwest Asia after the GW were at slight increased risk for any-cause hospitalization, whereas personnel deployed to Bosnia were at decreased risk for any-cause hospitalization (Smith et al., 2006b).

A systematic review of 20 studies on pain in GW veterans published between January 1990 and May 2004 concluded that a higher percentage of GW veterans reported symptoms of pain compared to a non-Gulf military comparison group. GW veterans were three times more likely to report abdominal pain than the non-Gulf group (Thomas et al., 2006a). Ang and co-workers conducted a follow-up in-person study of GW veterans who had been evaluated five years after the conflict. Family history, predeployment symptoms, and the level of perceived stress during their GW deployment were predictors of development of chronic widespread pain (Ang et al., 2006). Chapman and co-workers studied the sleep quality and the role of sleep medications for veterans with chronic pain. Their results suggest that depression may contribute more to sleep problems than pain and that additional studies of sleep medications in patients with chronic pain are needed (Chapman et al., 2006a). Kato and co-workers examined data from nearly 45,000 people in the Swedish Twin Registry on chronic widespread pain and comorbid conditions. Chronic widespread pain co-occurred with chronic fatigue, joint pain, depressive symptoms and irritable bowel syndrome. In co-twin analyses, odds ratios were not significant for psychiatric disorders but were significant for most of the other comorbidities (Kato et al., 2006).

Three groups studied motor vehicle accidents among GW veterans. Gackstetter and co-workers concluded that there was no association between possible nerve agent exposure at Khamisiyah and postwar fatal motor vehicle crashes among GW veterans (Gackstetter et al., 2006). A study by Hooper and co-workers of fatal motor vehicle between 1991 and 1995 in a cohort of GW era veterans suggested that demographic, military, and behavioral characteristics of deployed healthy warriors are similar to the risk profile for fatal motor vehicle crashes (Hooper et al., 2006). Lincoln and co-workers compared fatal motor vehicle crashes among veterans deployed to the GW and those who were not deployed. The annual rate of fatal motor vehicle crashes for GW veterans was significantly greater than that for nondeployed veterans. They also found a greater proportion of alcohol-related crashes among the GW veterans during the late night and early morning hours (Lincoln et al., 2006b).

GW veterans have an increased risk of fibromyalgia (Eisen et al., 2005; Lincoln et al., 2006b). Although there were no publications on GW veterans with fibromyalgia in 2006, seven papers were published on new treatments for fibromyalgia in the general population. Treatments studied were cognitive-behavioral therapy for sleep disturbance (Edinger et al., 2005), operant and cognitive behavioral treatments for pain (Thieme et al., 2006), milnacipran for pain and other symptoms (Gendreau et al., 2005), antioxidants vitamins such as vitamins C and E to decrease the severity of pain (Altindag and Celik, 2006), complementary and alternative medical therapies (Sarac and Gur, 2006), and repetitive transcranial magnetic stimulation for pain (Sampson et al., 2006). Some of these treatments appeared promising in the general population and may prove beneficial for ill GW veterans.

Thomas and co-workers systematically reviewed studies on multi-symptom conditions in GW veterans published between January 1990 and May 2004 and concluded that GW deployment was most strongly associated with CFS (Thomas et al., 2006b). Two papers published in 2006 dealt with CFS in GW veterans. Kelsall and co-workers studied CFS in Australian GW veterans and concluded that medically unexplained chronic fatigue was more common in veterans than in the comparison group (Kelsall et al., 2006).

Capuron and colleagues demonstrated a strong concordance between subjective complaints of mental fatigue and objective measurement of cognitive impairment in CFS patients; the authors suggest that heterogeneity in cognitive impairment in CFS patients between studies may be the result of differences in mental fatigue (Capuron et al.,

2006). Several studies have suggested a role for alterations in immunomodulation (Carmel et al., 2006; Jerjes et al., 2006b; Rajeevan et al., 2006; Smith et al., 2006a), inflammatory response (Carlo-Stella et al., 2006), and defects in T-cell activation (Jerjes et al., 2006a; Maes et al., 2006; Maher et al., 2005; Siegel et al., 2006) as underlying contributors to CFS. Studies of genetic polymorphisms in CFS patients support these suggestions (Carmel et al., 2006; Fang et al., 2006; Smith et al., 2006a; Whistler et al., 2006). Several papers published in 2006 identified potential new treatments for CFS. The results of one study suggested that patients with CFS might respond to treatment with omega-3 polyunsaturated fatty acids (Maes et al., 2005). A study of methylphenidate, an amphetamine derivative, found it significantly better than placebo in relieving fatigue and concentration disturbances in some patients with CFS (Blockmans et al., 2006). Researchers may wish to explore these treatments in GW veterans with CFS.

F. Abstracts from Published Research

Ahn KC, Ma SJ, Tsai HJ, Gee SJ, Hammock BD (2006) An immunoassay for a urinary metabolite as a biomarker of human exposure to the pyrethroid insecticide permethrin. Anal Bioanal Chem 384:713-722. (DoD-134)

Abstract: Permethrin is the most popular synthetic pyrethroid insecticide used in agriculture and public health. For the assessment of human exposure to permethrin, a competitive indirect enzyme-linked immunosorbent assay (ELISA) for the detection of the glycine conjugate of a major metabolite, cis-/trans-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropane-1-carboxylic acid (DCCA), of permethrin was developed based on a polyclonal antibody. An assay based on an antibody with a high sensitivity was optimized and characterized. The IC50 value and the detection range for trans-DCCA-glycine, in the assay buffer were 1.2 and 0.2-7.0 μg/L, respectively. The antibody recognized trans-DCCA-glycine and the mixture of cis-/trans-DCCA-glycine with an isomer range from 30:70 to 50:50 nearly equally. Little or no cross-reactivity to permethrin and its other free metabolites or glycine conjugates was measured. The integration of the ELISA and solid-phase extraction which was used to reduce the matrix effect from human urine samples provided for analysis of total cis-/trans-DCCA-glycine at low parts per billion levels in the samples. The limit of quantitation of the target analyte was 1.0 μg/L in urine with a limit of detection of 0.1 μg/L in buffer. This assay might be a useful tool for monitoring human exposure to permethrin.

Allen JS, Skowera A, Rubin GJ, Wessely S, Peakman M (2006) Long-lasting T cell responses to biological warfare vaccines in human vaccinees. Clin Infect Dis 43:1-7. (DoD-151)

Abstract: BACKGROUND: Medical countermeasures against biological warfare include the use of vaccines for anthrax and plague, which require repeated dosing and adjuvant to achieve adequate protection from threats such as inhalational anthrax and pneumonic plague. Despite the widespread use of these measures in preparation for recent military deployments, little is known about the cell-mediated immune response that is induced by these vaccines, in comparison with conventional vaccines, such as pertussis or tetanus-diphtheria vaccines. METHODS: To examine this question, we used cytokine enzyme-linked immunospot assays to measure interferon-gamma, interleukin (IL)-2, IL-4, and IL-13-producing cells in military service personnel vaccinated during the GW of 1990-1991. RESULTS: Our data indicate that 12-15 years after vaccination against anthrax and plague, antigen-specific T cell recall responses are present in the circulation and are comparable in magnitude to those for tetanus-diphtheria toxoids. Recall responses to anthrax were an approximately equal mixture of type 1 T helper cell (interferon-gamma and IL-2) and type 2 T helper cell (predominantly IL-13) responses, whereas plague cellular immunity was more polarized toward type 1 T helper cell responses. Responder cell frequency and type were similar to that against conventional tetanus-diphtheria (mixed type 1 and type 2 T helper cells) vaccine. When veterans were divided according to whether or not they reported multisymptom illness, there was no difference in the frequency or type of cellular response, although the number of cases in each group was small, and these data should be interpreted as preliminary. CONCLUSIONS: This study shows that, despite any putative limitations of vaccines for anthrax and plague in terms of achieving protective host immunity, long-lasting cell-mediated responses are generated with these agents.

Altindag O, Celik H (2006) Total antioxidant capacity and the severity of the pain in patients with fibromyalgia. Redox Rep 11:131-135.
Abstract: The purpose of the study was to determine the oxidative and antioxidative status of plasma in patients with fibromyalgia. Total antioxidant capacity (TAC) of plasma was significantly lower in patients with fibromyalgia (n = 20) than in healthy controls (n = 20) [1.5 (SD 0.3) and 1.9 (SD 0.3) mmol Trolox equiv/l, P = 0.001]. In contrast, the total peroxide level of plasma was significantly higher in patients than in healthy controls [37.4 (SD 6.7) and 33.0 (SD 2.7) µmol H_2O_2/l; P = 0.01]. The oxidative stress index (OSI) level was significantly higher in patients with fibromyalgia than in healthy controls [2.5 (SD 1.0) and 1.8 (SD 0.4); P = 0.007]. A significant negative correlation between visual analogue scale (VAS) and TAC level was determined (r = -0.79, P < 0.001). The present results indicate that patients with fibromyalgia are exposed to oxidative stress and this increased oxidative stress may play a role in the etiopathogenesis of the disease. Supplementation of antioxidant vitamins such as vitamins C and E to the therapy may be indicated.

Ang DC, Peloso PM, Woolson RF, Kroenke K, Doebbeling BN (2006) Predictors of incident chronic widespread pain among veterans following the first Gulf War. Clin J Pain 22:554-563. (DoD-058, HHS-001)
Abstract: OBJECTIVE: We sought to determine the predictors of incident chronic widespread pain (CWP), specifically, the effect of preexisting symptoms, stress, and psychosocial factors in the subsequent development of CWP among veterans from the first Gulf War (GW). METHODS: We conducted a structured telephone survey (baseline) of military personnel originally from Iowa who were either eligible for or deployed to Operation Desert Shield/Desert Storm, approximately 5 years postconflict. We conducted a follow-up, clinical, in-person study of those who met a priori-defined outcomes of symptoms of cognitive dysfunction, depression, or CWP, and also a sample of those who did not meet any of the outcomes of interest. RESULTS: A total of 370 of 602 evaluated GW veterans were free of CWP 5 years postconflict. At follow-up, 69 (19%) of these had developed CWP. A positive family history of medically unexplained persistent symptoms [odds ratio (OR)=4.8 (2.3, 13.2)] was strongly associated with CWP. At baseline, individuals who reported preexisting symptoms of bronchitis [OR=4.9 (1.9, 12.3)] and cognitive dysfunction [OR=2.1 (1.1, 4.2)] were more likely to develop CWP. Alcohol use [OR=0.2 (0.1, 0.7)] was protective against CWP. Rather than combat-related exposure per se, the perception of stress at the time of the GW [OR=1.6 (1.1, 2.3)] correlated with CWP. DISCUSSION: Among the GW veterans evaluated longitudinally in this study, family history, predeployment symptoms, and the level of perceived stress during the GW were associated with subsequent development of CWP.

Arfsten DP, Schaeffer DJ, Johnson EW, Robert CJ, Still KR, Wilfong ER (2006) Evaluation of the effect of implanted depleted uranium on male reproductive success, sperm concentration, and sperm velocity. Environ Res 100:205-215. (Funded by DoD)
Abstract: Depleted uranium (DU) projectiles have been used in battle in Iraq and the Balkans and will continue to be a significant armor-penetrating munition for the US military. As demonstrated in the Persian Gulf War, battle injury from DU projectiles and shrapnel is a possibility, and removal of embedded DU fragments from the body is not always practical because of their location in the body or their small size. Previous studies in rodents have demonstrated that implanted DU mobilizes and translocates to the gonads, and natural uranium may be toxic to spermatozoa and the male reproductive tract. In this study, the effects of implanted DU pellets on sperm concentration, motility, and male reproductive success were evaluated in adult (P1) Sprague-Dawley rats implanted with 0, 12, or 20, DU pellets of 1x2 mm or 12 or 20 tantalum (Ta) steel pellets of 1x2 mm. Twenty DU pellets of 1x2 mm (760 mg) implanted in a 500-g rat are equal to approximately 0.2 pound of DU in a 154-lb (70-kg) person. Urinary analysis found that male rats implanted with DU were excreting uranium at postimplantation days 27 and 117 with the amount dependent on dose. No deaths or evidence of toxicity occurred in P1 males over the 150-day postimplantation study period. When assessed at postimplantation day 150, the concentration, motion, and velocity of sperm isolated from DU-implanted animals were not significantly different from those of sham surgery controls. Velocity and motion of sperm isolated from rats treated with the positive control compound alpha-chlorohydrin were significantly reduced compared with sham surgery controls. There was no evidence of a detrimental effect of DU implantation on mating success at 30-45 days and 120-145 days postimplantation. The results of this study suggest that implantation of up to 20 DU pellets of 1x2 mm in rats for approximately 21% of their adult lifespan does not have an adverse impact on male reproductive success, sperm concentration, or sperm velocity.

Arguelles LM, Afari N, Buchwald DS, Clauw DJ, Furner S, Goldberg J (2006) A twin study of posttraumatic stress disorder symptoms and chronic widespread pain. Pain 124:150-157.
Abstract: Previous studies of the association between posttraumatic stress disorder (PTSD) and chronic widespread pain (CWP) or fibromyalgia have not examined the role of familial or genetic factors. The goals of this study were to determine if symptoms of PTSD are related to CWP in a genetically informative community-based sample of twin pairs, and if so, to ascertain if the association is due to familial or genetic factors. Data were obtained from the University of Washington Twin Registry, which contains 1042 monozygotic and 828 dizygotic twin pairs. To assess the symptoms of PTSD, we used questions from the Impact of Events Scale (IES). IES scores were partitioned into terciles. CWP was defined as pain located in 3 body regions lasting at least 1 week during the past 3 months. Random-effects regression models, adjusted for demographic features and depression, examined the relationship between IES and CWP. IES scores were strongly associated with CWP ($P<0.0001$). Compared to those in the lowest IES tercile, twins in the highest tercile were 3.5 times more likely to report CWP. Although IES scores were associated with CWP more strongly among dizygotic than among monozygotic twins, this difference was not significant. Our findings suggest that PTSD symptoms, as measured by IES, are strongly linked to CWP, but this association is not explained by a common familial or genetic vulnerability to both conditions. Future research is needed to understand the temporal association of PTSD and CWP, as well as the physiological underpinnings of this relationship.

Baireddy P, Mirajkar N, Nallapaneni A, Singleton N, Pope CN (2006) Effects of combined, multiple stressors on pyridostigmine-induced acute toxicity in rats. Arch Toxicol. (DOD-107)
Abstract: A number of studies have evaluated the possibility that stress-induced changes in blood-brain barrier permeability enhanced the central effects of the carbamate acetylcholinesterase inhibitor, pyridostigmine. We previously found relatively little evidence of stress-induced changes in the acute toxicity of pyridostigmine in rats using a variety of restraint, forced running and forced swimming stress conditions. In this study, we evaluated the effects of sequential pre-exposure to multiple stressors on the acute toxicity of pyridostigmine. Rats (n = 8 per treatment group) were either un-stressed or stressed by restraint (60 min), forced running (60 min, 15 m/min, 6 degrees incline) and forced swimming (15 min), and then given either vehicle (saline, 1 ml/kg, po) or pyridostigmine (30 mg/kg, po) immediately after the final stressor. Functional signs of cholinergic toxicity (involuntary movements, autonomic dysfunction) were recorded at 0.5, 1 and 2 h after dosing. Body temperature was measured both before stress and 2 h after dosing. Rats were sacrificed immediately after 2-h functional observations to collect tissues (whole blood, diaphragm, frontal cortex, hippocampus and cerebellum) for measurement of cholinesterase activity. Stressed rats treated with pyridostigmine exhibited higher lethality (2/8) compared to unstressed rats given pyridostigmine (0/8). Pyridostigmine elicited classical signs of cholinergic toxicity, but the rats that died did not show increased cholinergic signs and no significant differences in cholinergic signs were noted between treatment groups. Cholinesterase activity was significantly inhibited in blood (47-50%) and diaphragm (80%) following pyridostigmine exposure regardless of stress conditions. Slight but significant inhibition (11-15%) of cerebellar cholinesterase activity was observed following pyridostigmine exposure, but inhibition was not influenced by stress. We conclude that while acute lethality from pyridostigmine may be increased by combined, multiple stressors, increased lethality does not appear due to enhanced cholinergic toxicity or via increased cholinesterase inhibition in either central or peripheral tissues.

Black DW, Blum N, Letuchy E, Carney DC, Forman-Hoffman VL, Doebbeling BN (2006) Borderline personality disorder and traits in veterans: psychiatric comorbidity, healthcare utilization, and quality of life along a continuum of severity. CNS Spectr 11:680-689. (DoD-058 and HHS-001)
Abstract: OBJECTIVE: To examine the presence of borderline personality disorder (BPD) traits in Gulf War veterans, and to assess psychiatric comorbidity, health status, healthcare utilization, and quality of life (QOL) along a continuum of BPD trait severity. METHOD: BPD and traits were evaluated using the Schedule for Non-Adaptive and Adaptive Personality in 576 veterans who were either deployed to the Persian Gulf (1990-1991) or were on active duty though not deployed to the Gulf. Demographic and military characteristics, personal and family history, psychiatric comorbidity, and QOL were also assessed. RESULTS: One or more BPD traits were present in 247 subjects (43%), and BPD (>5 traits) was identified in 15 subjects (3%). The number of traits was significantly associated with age and level of education. Lifetime psychiatric comorbidity was significantly associated with the number of BPD traits present, and level of functioning, health status, healthcare utilization, social functioning, self-injurious tendencies, and military/behavioral problems. CONCLUSION: BPD and traits identified in Gulf War

veterans were associated with significant psychiatric morbidity, poorer QOL, and increased utilization of healthcare resources. Early recognition and treatment of veterans with BPD symptoms may be warranted to minimize the burden on the healthcare system.

Blanchard MS, Eisen SA, Alpern R, Karlinsky J, Toomey R, Reda DJ, Murphy FM, Jackson LW, Kang HK (2006) Chronic multisymptom illness complex in Gulf War I veterans 10 years later. Am J Epidemiol 163:66-75. (VA-002C)
Abstract: Prior research has demonstrated that shortly after the 1991 Gulf War (Gulf War I), chronic multisymptom illness (CMI) was more common among deployed veterans than among nondeployed veterans. The aims of the current study were to determine the prevalence of CMI among deployed and nondeployed veterans 10 years after Gulf War I, compare the distribution of comorbid conditions, and identify prewar factors associated with CMI. Cross-sectional data collected from1,061 deployed veterans and 1,128 nondeployed veterans examined between 1999 and 2001 were analyzed. CMI prevalence was 28.9% among deployed veterans and 15.8% among nondeployed veterans (odds ratio = 2.16, 95% confidence interval: 1.61, 2.90). Deployed and nondeployed veterans with CMI had similarly poorer quality-of-life measures and higher prevalences of symptom-based medical conditions, metabolic syndrome, and psychiatric disorders. Diagnoses of prewar anxiety disorders (not related to post-traumatic stress disorder) and depression were associated with CMI among both deployed and nondeployed veterans. Nicotine dependence and veteran-reported physician-diagnosed infectious mononucleosis were associated with CMI among deployed veterans, and migraine headaches and gastritis were associated with CMI among nondeployed veterans. CMI continues to be substantially more prevalent among deployed veterans than among nondeployed veterans 10 years after Gulf War I, but it manifests similarly in both groups. It is likely to be a common, persistent problem among veterans returning from the current Gulf War.

Blockmans D, Persoons P, Van HB, Bobbaers H (2006) Does methylphenidate reduce the symptoms of chronic fatigue syndrome? Am J Med 119:167-30.
Abstract: PURPOSE: Chronic fatigue syndrome is a clinical entity consisting of prolonged and debilitating fatigue in which concentration disturbances are very frequent. Until now, no medical treatment has shown any efficacy. The objectives of this study were to investigate the short-term effects of methylphenidate, an amphetamine derivative, on fatigue, concentration disturbances, and quality of life. SUBJECTS AND METHODS: A double-blind randomized placebo-controlled crossover study was conducted in 60 patients who fulfilled the 1994 Centers for Disease Control criteria for chronic fatigue syndrome and had concentration difficulties. Patients were enrolled between March 2003 and March 2004 at the outpatient department of a university hospital referral center for chronic fatigue syndrome patients. Random assignment to 4 weeks treatment with methylphenidate 2 x 10 mg/day, followed by 4 weeks of placebo treatment, or 4 weeks of placebo treatment, followed by methylphenidate treatment. Fatigue and concentration were measured with a Checklist Individual Strength (CIS) and a Visual Analogue Scale (VAS). RESULTS: Fatigue scores fell significantly during methylphenidate intake in comparison with baseline (mean difference: -0.7, P = .010 for VAS; mean difference: -11.8, P <.0001 for CIS) and in comparison with placebo (mean difference: -1.0, P = .001 for VAS; mean difference: -9.7, P <.0001 for CIS). Concentration disturbances, measured with a VAS improved significantly under methylphenidate treatment compared with baseline (mean difference: -1.3, P <.0001) and compared with placebo (mean difference: -1.1, P <.0001). A clinical significant effect (> or =33% improvement or CIS < or =76) on fatigue was achieved in 17% of patients, who were considered responders; on concentration in 22% of patients. CONCLUSIONS: Methylphenidate at a dose of 2 x 10 mg/day is significantly better than placebo in relieving fatigue and concentration disturbances in a minority of chronic fatigue syndrome patients. Further studies are needed to investigate the long-term effects of this treatment.

Capuron L, Welberg L, Heim C, Wagner D, Solomon L, Papanicolaou DA, Craddock RC, Miller AH, Reeves WC (2006) Cognitive dysfunction relates to subjective report of mental fatigue in patients with chronic fatigue syndrome. Neuropsychopharmacology 31:1777-1784.
Abstract: Patients with chronic fatigue syndrome (CFS) frequently complain of cognitive dysfunction. However, evidence of cognitive impairment in CFS patients has been found in some, but not other, studies. This heterogeneity in findings may stem from the relative presence of mental fatigue in the patient populations examined. The present study assessed this possibility in a population-based sample of CFS patients. In all, 43 patients with CFS defined by the criteria of the 1994 research case definition using measurements recommended by the 2003 International CFS Study Group, and 53 age-, sex-, and race/ethnicity-matched nonfatigued subjects were included in the study. Mental fatigue was assessed using the mental fatigue subscale of the multidimensional fatigue inventory. Cognitive function was evaluated using an automated battery of computerized tests (Cambridge neuropsychological test automated

battery (CANTAB)) that assessed psychomotor function, planning and problem-solving abilities, and memory and attentional performance. CFS patients with significant complaints of mental fatigue (score of mental fatigue 2 standard deviations above the mean of nonfatigued subjects) exhibited significant impairment in the spatial working memory and sustained attention (rapid visual information processing) tasks when compared to CFS patients with low complaints of mental fatigue and nonfatigued subjects. In CFS patients with significant mental fatigue, sustained attention performance was impaired only in the final stages of the test, indicating greater cognitive fatigability in these patients. CFS patients with low mental fatigue displayed performance comparable to nonfatigued subjects on all tests of the CANTAB battery. These findings show strong concordance between subjective complaints of mental fatigue and objective measurement of cognitive impairment in CFS patients and suggest that mental fatigue is an important component of CFS-related cognitive dysfunction.

Carlo-Stella N, Badulli C, De SA, Bazzichi L, Martinetti M, Lorusso L, Bombardieri S, Salvaneschi L, Cuccia M (2006) A first study of cytokine genomic polymorphisms in CFS: Positive association of TNF-857 and IFN-? 874 rare alleles. Clin Exp Rheumatol 24:179-182.
Abstract: OBJECTIVE: In the past two years we have developed a biological bank of genomic DNA, cDNA, serum and red blood cells of Italian patients with certified CFS from the two Italian referral centers for the syndrome. Recent studies have shown an imbalance in cytokine production in disease states similar to Chronic Fatigue Syndrome (CFS), such as sickness behavior, both in animals and in humans. However we notice that serum cytokine concentrations are often inconstant and degrade rapidly. With this in mind, we investigated cytokine gene polymorphisms in 80 Italian patients with CFS in order to ascertain whether in this group of patients it is possible to describe a genetic predisposition to an inflammatory response. METHODS: We analyzed the promoter polymorphisms of IL-10, IL-6 and the IFN-? 874 T/A polymorphism in intron 1 with a PCR-SSP method (Cytogen One Lambda Inc. Canoga Park, CA, U.S.A) in 54 patients and TNF-308 G/A and -857 C/T promoter polymorphisms with a PCR-RFLP method (in 54 and 80 patients respectively). RESULTS: There is a highly significant increase of TNF -857 TT and CT genotypes ($p = 0.002$) among patients with respect to controls and a significant decrease of IFN-? low producers (A/A) ($p = 0.04$) among patients with respect to controls. CONCLUSIONS: We hypothesize that CFS patients can have a genetic predisposition to an immunomodulatory response of an inflammatory nature probably secondary to one or more environmental insults of unknown nature.

Carmel L, Efroni S, White PD, Aslakson E, Vollmer-Conna U, Rajeevan MS (2006) Gene expression profile of empirically delineated classes of unexplained chronic fatigue. Pharmacogenomics 7:375-386.
Abstract: OBJECTIVES: To identify the underlying gene expression profiles of unexplained chronic fatigue subjects classified into five or six class solutions by principal component (PCA) and latent class analyses (LCA). METHODS: Microarray expression data were available for 15,315 genes and 111 female subjects enrolled from a population-based study on chronic fatigue syndrome. Algorithms were developed to assign gene scores and threshold values that signified the contribution of each gene to discriminate the multiclasses in each LCA solution. Unsupervised dimensionality reduction was first used to remove noise or otherwise uninformative gene combinations, followed by supervised dimensionality reduction to isolate gene combinations that best separate the classes. RESULTS: The authors' gene score and threshold algorithms identified 32 and 26 genes capable of discriminating the five and six multiclass solutions, respectively. Pair-wise comparisons suggested that some genes (zinc finger protein 350 [ZNF350], solute carrier family 1, member 6 [SLC1A6], F-box protein 7 [FBX07] and vacuole 14 protein homolog [VAC14]) distinguished most classes of fatigued subjects from healthy subjects, whereas others (patched homolog 2 [PTCH2] and T-cell leukemia/lymphoma [TCL1A]) differentiated specific fatigue classes. CONCLUSION: A computational approach was developed for general use to identify discriminatory genes in any multiclass problem. Using this approach, differences in gene expression were found to discriminate some classes of unexplained chronic fatigue, particularly one termed interoception.

Chapman JB, Lehman CL, Elliott J, Clark JD (2006) Sleep quality and the role of sleep medications for veterans with chronic pain. Pain Med 7:105-114.
Abstract: OBJECTIVE: The purpose of this study was to investigate the nature of sleep problems in veterans presenting to a pain clinic, factors that predict likelihood of being prescribed a sleep medication, types of medications prescribed, and the relationships between sleep medication use and sleep quality, pain, and depression. DESIGN/SETTING/PATIENTS: Participants were 201 consecutive patients referred to a Veterans Affairs outpatient pain clinic. They were administered the Pittsburgh Sleep Quality Index, Multidimensional Pain Inventory, and Beck Depression Inventory at intake and 2-month follow-up. Sleep and opioid medication prescriptions were also monitored. RESULTS: Pain severity did not predict global sleep quality; global sleep quality was not predictive

of pain severity. Greater depression predicted both more severe pain and more sleep impairment. Having previously been prescribed such medications was the only significant predictor of being prescribed a sleep medication at the time of the 2-month assessment. For the 45% of participants on sleep medications, these medications were not associated with any significant change in pain factors or depression. However, sleep medication use was associated with worse global sleep quality, sleep duration, and sleep efficiency. Opioid prescription was not a significant predictor of sleep factors, pain-related variables, or depression symptoms. DISCUSSION: Results suggest depression may contribute more significantly to sleep problems than pain-related variables in this population. The data suggest the need for controlled, prospective studies of sleep medication to further investigate the impact of sleep medications on sleep components in patients with chronic pain.

Chapman S, Kadar T, Gilat E (2006) Seizure duration following sarin exposure affects neuro-inflammatory markers in the rat brain. Neurotoxicology 27:277-283.
Abstract: The current study was aimed to characterize for the first time the alterations in the characteristic neuro-inflammatory markers triggered by sarin exposure in the rat's brain, and to investigate its dependency on seizure duration. Centrally mediated seizures are a common consequence of exposure to organophosphates (OP) despite conventional treatment with atropine and an oxime. In the present study midazolam, was used to control duration and intensity of seizures. The levels of the pro-inflammatory cytokine peptides IL-1ß, IL-6, TNF-a and prostaglandin E_2 (PGE_2) were monitored at various times after sarin exposure in the hippocampus and cortex of rats treated with midazolam following 5 or 30 min of seizure activity. Biochemical evaluation of brain tissues revealed a significant increase in the level of the pro-inflammatory peptides starting at 2 h and peaking at 2-24 h following sarin. Hippocampal values of IL1-ß increased from 1.2+/-0.1 pg/mg tissue (control), to 2.4+/-0.3 at 2 h (5 min seizure) and to 9.3+/-2.5 at 8h (30 min seizure). PGE_2 level in the hippocampus increased up to 24 h following exposure (from 56+/-3 to 175+/-26 and 277+/-28 pg/mg tissue) following 5 and 30 min of seizure activity respectively. Thus, unlike limitation of seizures to 5 min by midazolam, delayed treatment (30 min) resulted in prolonged seizures and pronounced increase in cytokines and PGE_2. In addition, a second increase in inflammatory markers was observed 30 days following sarin exposure only in rats treated following 30 min of seizure activity. Histological evaluation of the rat brain, conducted in this study, revealed lack of damage in the hippocampus and piriform cortex with minor lateral ventricles enlargement in few animals following 5 min of sarin-induced seizure activity. In contrast, marked histological damage to the brain was demonstrated following 30 min of seizure activity, consisting severe damage to the hippocampus, piriform cortex and some thalamic nuclei. In summary, a novel characterization of the prolonged central neuro-inflammatory process that accompanies sarin exposure is presented. The timing of the anticonvulsive treatment was shown to be crucial in modulation of the neuro-inflammatory response, and may implicate the consequent long-term brain damage.

Cherstniakova SA, Garcia GE, Strong J, Bi D, Weitz J, Roy MJ, Cantilena LR (2006) Rapid determination of N,N-diethyl-m-toluamide and permethrin in human plasma by gas chromatography-mass spectrometry and pyridostigmine bromide by high-performance liquid chromatography. J Anal Toxicol 30:21-26. (DoD-124)
Abstract: A rapid and highly sensitive gas chromatography-mass spectrometry (GC-MS) method for simultaneous determination of N,N-diethyl-m-toluamide (DEET) and permethrin with (2)H(10)-phenanthrene (98 atom %) as an internal standard and a separate external standard high-performance liquid chromatography (HPLC) method for pyridostigmine bromide (PB) determination in human plasma were developed and validated. The GC-MS method for DEET and permethrin quantification utilizes a one-step extraction with tert-butylmethylether. The HPLC method for PB quantification involves a solid-phase extraction and UV detection. The range of the analytical method for DEET and permethrin was 1 ng/mL to 100 ng/mL and for PB was 5 ng/mL to 100 ng/mL. Recovery from plasma proved to be more than 80%. The intraday precision ranged from 1.3% to 8% for DEET, from 2.1% to 11.4% for permethrin, and from 3.0% to 4.8% for PB. The interday precision was 3% for DEET, ranged from 5% to 9% for permethrin, and from 5% to 9% for PB. The accuracy for the limit of quantification was 92% +/- 8% relative standard deviation (RSD) for DEET, 112% +/- 11% RSD for permethrin, and 109% +/- 5% RSD for PB. All 3 compounds were stable in human plasma at -80 degrees C for at least 12 months and after 2 freeze-thaw cycles with RSD values ranging from 7.1% (DEET, 80 ng/mL) to 8.1% (DEET, 8 ng/mL), from 2.3% (permethrin, 80 ng/mL) to 11.6 % (permethrin, 8 ng/mL), and from 0.2% (PB, 80 ng/mL) to 3.6% (PB, 8 ng/mL). Both methods were successfully applied to pharmacokinetic/ pharmacodynamic studies of combined exposure of DEET (skin application), permethrin (treated uniforms), and PB (30 mg orally three times/day for four doses) in healthy volunteers (n = 81).

Chou CC, Yang JH, Chen SD, Monteiro-Riviere NA, Li HN, Chen JJ (2006) Expression profiling of human epidermal keratinocyte response following 1-minute JP-8 exposure. Cutan Ocul Toxicol 25:141-153.
Abstract: The cDNA microarray analysis of 9600 expressed sequence tags was performed to examine the gene expression changes in human epidermal keratinocytes after 1-minute JP-8 exposure; 151 genes were identified as JP-8 responsive and classified into 8 clusters by self organization map. Genes involved in basal transcription and translations were up-regulated, whereas genes related to DNA repair, metabolism, and keratin were mostly down-regulated. Genes encoded for growth factors, apoptosis, signal transduction, and adhesion were also altered. These results indicated that human keratinocyte responds to a single dose of JP-8 insult and revealed several cellular processes previously not associated with jet fuel exposure.

Coryell VH, Stearns DM (2006) Molecular analysis of hprt mutations generated in Chinese hamster ovary EM9 cells by uranyl acetate, by hydrogen peroxide, and spontaneously. Mol Carcinog 45:60-72.
Abstract: Naturally occurring uranium and depleted uranium (DU) are believed to be health hazards by virtue of both their chemical and radiological properties. The mechanism(s) behind uranium's chemotoxic effects has yet to be elucidated. Previous work has shown that DU, as uranyl acetate (UA), was mutagenic at the hypoxanthine (guanine) phosphoribosyltransferase (hprt) locus in XRCC1-deficient CHO EM9 cells. The purpose of the current study was to characterize the mutations induced by UA at the hprt locus of CHO EM9 cells and compare the mutation spectrum of UA with those of hydrogen peroxide and spontaneous mutations in the same line. The hypothesis being tested was that if DU as UA is chemically genotoxic then the mutation spectrum induced by the heavy metal should be distinct from that produced spontaneously or by H_2O_2. A total of 59 UA-induced, 38 spontaneous and 45 H_2O_2-induced mutations were identified. Base substitutions comprised 29%, 42%, and 16% of UA, spontaneous, and H_2O_2 mutants, respectively. The frequency of G --> T or C --> A substitutions was not significantly different in spontaneous or H_2O_2-induced mutants than in UA-induced mutants, suggesting a possible role for 8-oxodG damage in UA mutagenesis. However, the observation that UA produced significantly more major genomic rearrangements (multiexon insertions and deletions) than occurred spontaneously suggests the possibility that DNA strand breaks or crosslinks could also be UA-induced mutagenic lesions. The unique mutation spectrum elicited by exposure to UA suggests that UA generates mutations in ways that are different from spontaneous and free radical as well as radiological mechanisms.

Creamer M, Carboon I, Forbes AB, McKenzie DP, McFarlane AC, Kelsall HL, Sim MR (2006) Psychiatric disorder and separation from military service: a 10-year retrospective study. Am J Psychiatry 163:733-734.
(Funded by Australian Government-Department of Veterans' Affairs)
Abstract: OBJECTIVE: This study investigated the association between the onset of psychiatric morbidity and separation from military service over a 10-year period (1991-2001). METHOD: The prevalence of affective, anxiety, somatic, and substance use disorders was assessed in 2,215 male Australian Navy personnel with the Composite International Diagnostic Interview. RESULTS: The onset of a psychiatric disorder during military service was related to a 19% greater risk of separation overall. The majority of those leaving military service did so in the first year after symptom onset. Personnel who remained in service past this period had no significantly elevated risk of separation in subsequent years. CONCLUSIONS: Psychiatric morbidity represents a significant potential cost to defense forces. Improved recognition and early management of mental health problems among military personnel may improve retention rates.

Damodaran TV, Greenfield ST, Patel AG, Dressman HK, Lin SK, Abou-Donia MB (2006) Toxicogenomic studies of the rat brain at an early time point following acute sarin exposure. Neurochem Res 31:367-381.
Abstract: We have studied sarin-induced global gene expression patterns at an early time point (2 h: 0.5 x LD50) using Affymetrix Rat Neurobiology U34 chips and male Sprague-Dawley rats. A total of 46 genes showed statistically significant alterations from control levels. Three gene categories contained more of the altered genes than any other groups: ion channel (8 genes) and calcium channel and binding proteins (6 genes). Alterations were also found in the following gene groups: ATPases and ATP-based transporters (4), growth factors (4), G-protein-coupled receptor pathway-related molecules (3), neurotransmission and neurotransmitter transporters (3), cytoskeletal and cell adhesion molecules (2), hormones (2), mitochondria-associated proteins (2), myelin proteins (2), stress-activated molecules (2), cytokine (1), caspase (1), GABAnergic (1), glutamergic (1), immediate early gene (1), prostaglandin (1), transcription factor (1), and tyrosine phosphorylation molecule (1). Persistent alteration of the following genes also were noted: Arrb1, CaMKIIa, CaMKIId, Clcn5, IL-10, c-Kit, and Plp1, suggesting altered GPCR, kinase, channel, and cytokine pathways. Selected genes from the microarray data were further validated using relative RT-PCR. Some of those genes (GFAP, NF-H, CaMKIIa, Calm, and MBP) have been shown

by other laboratories and ours, to be involved in the pathogenesis of sarin-induced pathology and organophosphate-induced delayed neurotoxicity (OPIDN). Induction of both proapoptotic (Bcl2l11, Casp6) and antiapoptotic (Bcl-X) genes, besides suppression of p21, suggest complex cell death/protection-related mechanisms operating early on. Principal component analysis (PCA) of the expression data confirmed that the changes in gene expression are a function of sarin exposure, since the control and treatment groups separated clearly. Our model (based on current and previous studies) indicates that both degenerative and regenerative pathways are activated early and contribute to the level of neurodegeneration at a later time, leading to neuro-pathological alterations.

Damodaran TV, Patel AG, Greenfield ST, Dressman HK, Lin SM, Abou-Donia MB (2006) Gene expression profiles of the rat brain both immediately and 3 months following acute sarin exposure. Biochem Pharmacol 71:497-520.
Abstract: We have studied sarin-induced global gene expression patterns at an early time point (15 min; 0.5x LD_{50}) and a later time point (3 months; 1xLD_{50}) using Affymetrix: Rat Neurobiology U34 chips in male, Sprague-Dawley rats and have identified a total of 65 (early) and 38 (late) genes showing statistically significant alterations from control levels at 15 min and 3 months, respectively. At the early time point, those that are classified as ion channel, cytoskeletal and cell adhesion molecules, in addition to neuropeptides and their receptors predominated over all other groups. The other groups included: cholinergic signaling, calcium channel and binding proteins, transporters, chemokines, GABAnergic, glutamatergic, aspartate, catecholaminergic, nitric oxide synthase, purinergic, and serotonergic signaling molecules. At the late time point, genes that are classified as calcium channel and binding proteins, cytoskeletal and cell adhesion molecules and GABAnergic signaling molecules were most prominent. Seven molecules (Ania-9, Arrb-1, CX-3C, Gabab-1d, Nos-2a, Nrxn-1b, PDE2) were identified that showed altered persistent expression in both time points. Selected genes from each of these time points were further validated using semi quantitative RT-PCR approaches. Some of the genes that were identified in the present study have been shown to be involved in organophosphate-induced neurotoxicity by both other groups as well as ours. Principal component analysis (PCA) of the expression data from both time points was used for comparative analysis of the gene expression, which indicated that the changes in gene expression were a function of dose and time of euthanasia after the treatment. Our model also predicts that besides dose and duration of post-treatment period, age and possibly other factors may be playing important roles in the regulation of pathways, leading to the neurotoxicity.

Del Giudice G, Fragapane E, Bugarini R, Hora M, Henriksson T, Palla E, O'hagan D, Donnelly J, Rappuoli R, Podda A (2006) Vaccines with the MF59 adjuvant do not stimulate antibody responses against squalene. Clin Vaccine Immunol 13:1010-1013. (Italian study)
Abstract: Squalene is a naturally occurring oil which has been used in the development of vaccine adjuvants, such as the oil-in-water emulsion MF59. In past years, by use of noncontrolled and nonvalidated assays, a claim was made that antisqualene antibodies were detectable in the sera of individuals with the so-called Gulf War syndrome. Using a validated enzyme-linked immunosorbent assay for the quantitation of immunoglobulin G (IgG) and IgM antibodies against squalene, we demonstrated that antisqualene antibodies are frequently detectable at very low titers in the sera of subjects who were never immunized with vaccines containing squalene. More importantly, vaccination with a subunit influenza vaccine with the MF59 adjuvant neither induced antisqualene antibodies nor enhanced preexisting antisqualene antibody titers. In conclusion, antisqualene antibodies are not increased by immunization with vaccines with the MF59 adjuvant. These data extend the safety profile of the MF59 emulsion adjuvant.

Dobson AW, Lack AK, Erikson KM, Aschner M (2006) Depleted uranium is not toxic to rat brain endothelial (RBE4) cells. Biol Trace Elem Res 110:61-72. (DoD-126)
Abstract: Studies on Gulf War veterans with depleted uranium (DU) fragments embedded in their soft tissues have led to suggestions of possible DU-induced neurotoxicity. We investigated DU uptake into cultured rat brain endothelial cells (RBE4). Following the determination that DU readily enters RBE4 cells, cytotoxic effects were analyzed using assays for cell volume increase, heat shock protein 90 (Hsp90) expression, 3-[4,5-dimethylthiazol-2-yl]-2, 5-diphenyltetrazolium bromide (MTT) reduction, and lactate dehydrogenase (LDH) activity. The results of these studies show that uptake of the U_3O_8 uranyl chloride form of DU into RBE4 cells is efficient, but there are little or no resulting cytotoxic effects on these cells as detected by common biomarkers. Thus, the present experimental paradigm is rather reassuring and provides no indication for overt cytotoxicity in endothelial cells exposed to DU.

Doyle P, Maconochie N, Ryan M (2006) Reproductive health of Gulf War veterans. Philos Trans R Soc Lond B Biol Sci 361:571-584.

Abstract: In this review we summarize the scientific literature on reproductive health following deployment to the first Gulf war by armed service personnel. All the studies examined had methodological limitations, making interpretation difficult. Nonetheless we conclude that for male veterans there is no strong or consistent evidence to date for an effect of service in the first Gulf war on the risk of major, clearly defined, birth defects or stillbirth in offspring conceived after deployment. Effects on specific rare defects cannot be excluded at this stage since none of the studies had the statistical power to examine them. For miscarriage and infertility, there is some evidence of small increased risks associated with service, but the role of bias is likely to be strong. For female veterans, there is insufficient information to make robust conclusions, although the weight of evidence to date does not indicate any major problem associated specifically with deployment to the Gulf. None of the studies have been able to examine risk according particular exposures, and so possible associations with specific exposures for smaller groups of exposed veterans cannot be excluded.We suggest that the way forward to address the question of veterans' reproductive health with confidence in the future is prospective surveillance following deployment. Anything less will result in further problems of interpretation and continued anxiety for parents, as well as prospective parents, in the armed forces.

Dublineau I, Grison S, Grandcolas L, Baudelin C, Tessier C, Suhard D, Frelon S, Cossonnet C, Claraz M, Ritt J, Paquet P, Voisin P, Gourmelon P (2006) Absorption, accumulation and biological effects of depleted uranium in Peyer's patches of rats. Toxicology 227:227-239.

Abstract: The digestive tract is the entry route for radionuclides following the ingestion of contaminated food and/or water wells. It was recently characterized that the small intestine was the main area of uranium absorption throughout the gastrointestinal tract. This study was designed to determine the role played by the Peyer's patches in the intestinal absorption of uranium, as well as the possible accumulation of this radionuclide in lymphoid follicles and the toxicological or pathological consequences on the Peyer's patch function subsequent to the passage and/or accumulation of uranium. Results of experiments performed in Ussing chambers indicate that the apparent permeability to uranium in the intestine was higher (10-fold) in the mucosa than in Peyer's patches ((6.21+/-1.21 to 0.55+/-0.35)x10^{-6}cm/s, respectively), demonstrating that the small intestinal epithelium was the preferential pathway for the transmucosal passage of uranium. A quantitative analysis of uranium by ICP-MS following chronic contamination with depleted uranium during 3 or 9 months showed a preferential accumulation of uranium in Peyer's patches (1355% and 1266%, respectively, at 3 and 9 months) as compared with epithelium (890% and 747%, respectively, at 3 and 9 months). Uranium was also detected in the mesenteric lymph nodes (approximately 5-fold after contamination with DU). The biological effects of this accumulation of depleted uranium after chronic contamination were investigated in Peyer's patches. There was no induction of the apoptosis pathway after chronic DU contamination in Peyer's patches. The results indicate no change in the cytokine expression (Il-10, TGF-ß, IFN-?, TNF-a, MCP-1) in Peyer's patches and in mesenteric lymph nodes, and no modification in the uptake of yeast cells by Peyer's patches. In conclusion, this study shows that the Peyer's patches were a site of retention for uranium following the chronic ingestion of this radionuclide, without any biological consequences of such accumulation on Peyer's patch functions.

Dublineau I, Grison S, Linard C, Baudelin C, Dudoignon N, Souidi M, Marquette C, Paquet F, Aigueperse J, Gourmelon P (2006) Short-term effects of depleted uranium on immune status in rat intestine. J Toxicol Environ Health A 69:1613-1628.

Abstract: In the event of ingestion, the digestive tract is the first biological system exposed to depleted uranium (DU) intake via the intestinal lumen. However, little research has addressed the biological consequences of a contamination with depleted uranium on intestinal properties such as the barrier function and/or the immune status of this tissue. The aim of this study was to determine if the ingestion of depleted uranium led to changes in the gut immune system of the intestine. The experiments were performed at 1 and 3 d following a per os administration of DU to rats at sublethal dose (204 mg/kg). Several parameters referring to the immune status, such as gene and protein expressions of cytokines and chemokines, and localization and density of immune cell populations, were assessed in the intestine. In addition, the overall toxicity of DU on the small intestine was estimated in this study, with histological appearance, proliferation rate, differentiation pattern, and apoptosis process. Firstly, the results of this study indicated that DU was not toxic for the intestine, as measured by the proliferation, differentiation, and apoptosis processes. Concerning the immune properties of the intestine, the ingestion of depleted uranium induced some changes in the production of chemokines and in the expression of cytokines. A diminished production of monocyte chemoattractant protein-1 (MCP-1) was noted at 1 day post exposure. At 3 d, the increased gene

expression of interferon gamma (IFN-?) was associated with an enhanced mRNA level of Fas ligand, suggesting an activation of the apoptosis pathway. However, no increased apoptotic cells were observed at 3 d in the contaminated animals. There were no changes in the localization and density of neutrophils, helper T lymphocytes, and cytotoxic T lymphocytes after DU administration. In conclusion, these results suggest that depleted uranium is not toxic for the intestine after acute exposure. Nevertheless, DU seems to modulate the expression and/or production of cytokines (IFN-?) and chemokines (MCP-1) in the intestine. Further experiments need to be performed to determine if a chronic contamination at low dose leads in the long term to modifications of cytokines/chemokines patterns, and to subsequent changes in immune response of the intestine.

Edinger JD, Wohlgemuth WK, Krystal AD, Rice JR (2005) Behavioral insomnia therapy for fibromyalgia patients: a randomized clinical trial. Arch Intern Med 165:2527-2535.
Abstract: BACKGROUND: Insomnia is common and debilitating to fibromyalgia (FM) patients. Cognitive-behavioral therapy (CBT) is effective for many types of patients with insomnia, but has yet to be tested with FM patients. This study compared CBT with an alternate behavioral therapy and usual care for improving sleep and other FM symptoms. METHODS: This randomized clinical trial enrolled 47 FM patients with chronic insomnia complaints. The study compared CBT, sleep hygiene (SH) instructions, and usual FM care alone. Outcome measures were subjective (sleep logs) and objective (actigraphy) total sleep time, sleep efficiency, total wake time, sleep latency, wake time after sleep onset, and questionnaire measures of global insomnia symptoms, pain, mood, and quality of life. RESULTS: Forty-two patients completed baseline and continued into treatment. Sleep logs showed CBT-treated patients achieved nearly a 50% reduction in their nocturnal wake time by study completion, whereas SH therapy- and usual care-treated patients achieved only 20% and 3.5% reductions on this measure, respectively. In addition, 8 (57%) of 14 CBT recipients met strict subjective sleep improvement criteria by the end of treatment compared with 2 (17%) of 12 SH therapy recipients and 0% of the usual care group. Comparable findings were noted for similar actigraphic improvement criteria. The SH therapy patients showed favorable outcomes on measures of pain and mental well-being. This finding was most notable in an SH therapy subgroup that self-elected to implement selected CBT strategies. CONCLUSIONS: Cognitive-behavioral therapy represents a promising intervention for sleep disturbance in FM patients. Larger clinical trials of this intervention with FM patients seem warranted.

Eisen SA, Karlinsky J, Jackson LW, Blanchard M, Kang HK, Murphy FM, Alpern R, Reda DJ, Toomey R, Battistone MJ, Parks BJ, Klimas N, Pak HS, Hunter J, Lyons MJ, Henderson WG (2006) Spouses of Persian Gulf War I veterans: medical evaluation of a U.S. cohort. Mil Med 171:613-618. (VA-002C)
Abstract: Ten years after the 1991 Persian Gulf War (GW I), a comprehensive evaluation of a national cohort of deployed veterans (DV) demonstrated a higher prevalence of several medical conditions, in comparison to a similarly identified cohort of nondeployed veterans (NDV). The present study determined the prevalence of medical conditions among nonveteran spouses of these GW I DV and NDV. A cohort of 490 spouses of GW I DV and 537 spouses of GW I NDV underwent comprehensive face-to-face examinations. No significant differences in health were detected except that spouses of DV were less likely to have one or more of a group of six common skin conditions. We conclude that, 10 years after GW I, the general physical health of spouses of GW I DV is similar to that of spouses of NDV.

El-Masry EM, Abou-Donia MB (2006) Interaction of pyridostigmine bromide and N,N-diethyl-m-toluamide alone and in combination with P-glycoprotein expressed in Escherichia coli leaky mutant. J Toxicol Environ Health A 69:919-933.
Abstract: P-glycoprotein (P-gp), the most extensively studied ATP-binding transporter, functions as a biological barrier by extruding toxic substances and xenobiotics out of the cell. This study was carried out to determine the effect of N,N-diethyl-m-toluamide (DEET) and pyridostigmine bromide (PB), alone and in combination, on P-gp expression using Escherichia coli leaky mutant transformed with Mdr1 gene (pT5-7/mdr1), which codes for P-gp or lactose permease (pT5-7/lacY) as negative control. Also, daunomycin (a known P-gp substrate) was used as a positive control and reserpine (a known P-gp inhibitor) served as a negative control. An in vitro cell-resistant assay was used to monitor the potential of test compounds to interact with P-gp. Following exposure of the cells to pyridostigmine bromide or daunomycin, P-gp conferred significant resistance against both compounds, while reserpine and DEET significantly inhibited the glycoprotein. Cells were grown in the presence of noncytotoxic concentrations of daunomycin, pyridostigmine bromide, reserpine, or DEET, and membrane fractions were examined by Western immunoblotting for expression of P-gp. Daunomycin induced P-gp expression quantitatively more than pyridostigmine bromide, while reserpine and DEET significantly inhibited P-gp expression in cells

harboring mdr1. Photoaffinity labeling experiment performed with the P-gp ligand [125I]iodoarylazidoprazosin demonstrated that compounds that induced or inhibited P-gp transport activity also bound to P-gp. DEET was also found to be a potent inhibitor of P-gp-mediated ATPase activity, whereas pyridostigmine bromide increased P-gp ATPase activity. Cells expressing P-gp or lac permease were exposed to pyridostigmine bromide and DEET, alone and in combination. Noncytotoxic concentrations of DEET significantly inhibited P-gp-mediated resistance against pyridostigmine bromide, resulting in a reduction of the number of effective drug interactions with biological targets. An explanation of these results might be that DEET is a third-generation inhibitor of P-gp; it has high potency and specificity for P-gp, it inhibits hydrolysis of ATP, it exerts no appreciable impact on cytochrome P-450 3A4, and it prevents transport of xenobiotics, such as pyridostigmine bromide, out of the cell. This conclusion explains, at least in part, the increased toxicity and bioavailability of pyridostigmine bromide following combined administration with DEET. This study improves our understanding of the basis of chemical interactions with DEET by defining the ability of drugs to interact with P-gp either as inhibitors or substrates, which may in turn lead to altered efficacy or toxicity.

English BA, Jewell M, Jewell G, Ambrose S, Davis LL (2006) Treatment of chronic posttraumatic stress disorder in combat veterans with citalopram: an open trial. J Clin Psychopharmacol 26:84-88.
Abstract: Posttraumatic stress disorder (PTSD) is a serious mental illness which exhibits significant impairment of psychosocial and occupational function. At present, serotonin reuptake inhibitors (SRIs) show therapeutic promise for the treatment of PTSD. However, results in the veteran population have been less robust or often negative. In this study, a relatively new and the most selective SRI, citalopram, was evaluated for the treatment of PTSD. Veterans with chronic PTSD (N = 18) were enrolled in an 8-week open trial of citalopram after providing written informed consent. The primary outcome measures were the Clinician-Administered PTSD Scale (CAPS), the Hamilton Rating Scale for Anxiety (HAM-A), and the Clinical Global Impression Scale (CGI). Seventeen patients completed at least 4 weeks of the 8-week trial. During treatment, there was a moderate response with 42% of patients demonstrating a > or =30% reduction in total CAPS score at week 8. Comparable results were demonstrated in the Hamilton Depression Rating Scale (HAM-D), HAM-A, Global Assessment of Function (GAF), and CGI rating scales. In a follow-up analysis, a treatment effect was shown for CAPS B at week 4, but was not sustained at week 8. Overall, citalopram was generally well tolerated with reported adverse events being benign in nature. These pilot results demonstrate a moderate effect of citalopram in the treatment of combat-induced PTSD. However, the sample size was small and patient population is limited to veterans with combat-induced PTSD. Further study in a larger and more diverse patient sample is warranted prior to final conclusions on efficacy of citalopram for the treatment of PTSD.

Fang H, Xie Q, Boneva R, Fostel J, Perkins R, Tong W (2006) Gene expression profile exploration of a large dataset on chronic fatigue syndrome. Pharmacogenomics 7:429-440.
Abstract: OBJECTIVE: To gain understanding of the molecular basis of chronic fatigue syndrome (CFS) through gene expression analysis using a large microarray data set in conjunction with clinically administrated questionnaires. METHOD: Data from the Wichita (KS, USA) CFS Surveillance Study was used, comprising 167 participants with two self-report questionnaires (multidimensional fatigue inventory [MFI] and Zung depression scale [Zung]), microarray data, empiric classification, and others. Microarray data was analyzed using bioinformatics tools from ArrayTrack. RESULTS: Correspondence analysis was applied to the MFI questionnaire to select the 23 samples having either the most or the least fatigue, and to the Zung questionnaire to select the 26 samples having either the most or least depression; ten samples were common, resulting in a total of 39 samples. The MFI and Zung-based CFS/non-CFS (NF) classifications on the 39 samples were consistent with the empiric classification. Two differentially-expressed gene lists were determined, 188 fatigue-related genes and 164 depression-related genes, which shared 24 common genes and involved 11 common pathways. Principal component analysis based on 24 genes clearly separates 39 samples with respect to their likelihood to be CFS. Most of the 24 genes are not previously reported for CFS, yet their functions are consistent with the prevailing model of CFS, such as immune response, apoptosis, ion channel activity, signal transduction, cell-cell signaling, regulation of cell growth and neuronal activity. Hierarchical cluster analysis was performed based on 24 genes to classify 128 (=167-39) unassigned samples. Several of the 11 identified common pathways are supported by earlier findings for CFS, such as cytokine-cytokine receptor interaction and neuroactive ligand-receptor interaction. Importantly, most of the 11 common pathways are interrelated, suggesting complex biological mechanisms associated with CFS. CONCLUSION: Bioinformatics is critical in this study to select definitive sample groups, analyze gene expression data and gain insight into biological mechanisms. The 24 identified common genes and 11 common pathways could be important in future studies of CFS at the molecular level.

Fiedler N, Ozakinci G, Hallman W, Wartenberg D, Brewer NT, Barrett DH, Kipen HM (2006) Military deployment to the Gulf War as a risk factor for psychiatric illness among US troops. Br J Psychiatry 188:453-459. (HHS-006 and National Institute of Environmental Health Sciences)
Abstract: BACKGROUND: Several studies document an excess of psychiatric symptoms among veterans of the 1991 Gulf War. However, little is known about the prevalence of psychiatric disorders in those who were deployed to that conflict. AIMS: To compare the 12-month prevalence and associated risk factors for DSM Axis I psychiatric diagnoses between random samples of Gulf War-deployed veterans and veterans of the same era not deployed to the Persian Gulf (era veterans). METHOD: Interview data from 967 Gulf War veterans and 784 era veterans were examined to determine current health status, medical conditions, symptoms and Axis I psychiatric disorders. Logistic regression models evaluated risk factors for psychiatric disorder. RESULTS: Gulf War veterans had a significantly higher prevalence of psychiatric diagnoses, with twice the prevalence of anxiety disorders and depression. Lower rank, female gender and divorced or single marital status were significant independent predictors of psychiatric disorder. CONCLUSIONS: Deployment to the Gulf War is associated with a range of mental health outcomes more than 10 years after deployment.

Fitsanakis VA, Erikson KM, Garcia SJ, Evje L, Syversen T, Aschner M (2006) Brain accumulation of depleted uranium in rats following 3- or 6-month treatment with implanted depleted uranium pellets. Biol Trace Elem Res 111:185-197. (DoD-126)
Abstract: Depleted uranium (DU) is used to reinforce armor shielding and increase penetrability of military munitions. Although the data are conflicting, DU has been invoked as a potential etiological factor in Gulf War syndrome. We examined regional brain DU accumulation following surgical implantation of metal pellets in male Sprague-Dawley rats for 3 or 6 mo. Prior to surgery, rats were randomly divided into five groups: Nonsurgical control (NS Control); 0 DU pellets/20 tantalum (Ta) pellets (Sham); 4 DU pellets/16 Ta pellets (Low); 10 DU pellets/10 Ta pellets (Medium); 20 DU pellets/0 Ta pellets (High). Rats were weighed weekly as a measure of general health, with no statistically significant differences observed among groups in either cohort. At the conclusion of the respective studies, animals were perfused with phosphate-buffered saline, pH 7.4, to prevent contamination of brain tissue with DU from blood. Brains were removed and dissected into six regions: cerebellum, brainstem (pons and medulla), midbrain, hippocampus, striatum, and cortex. The uranium content was measured in digested samples as its 238U isotope by high-resolution inductively coupled plasma-mass spectrometry. After 3 mo postimplantation, DU significantly accumulated in all brain regions except the hippocampus in animals receiving the highest dose of DU ($p < 0.05$). By 6 mo, however, significant accumulation was measured only in the cortex, midbrain, and cerebellum ($p < 0.01$). Our data suggest that DU implanted in peripheral tissues can preferentially accumulate in specific brain regions.

Fukuda S, Ikeda M, Chiba M, Kaneko K (2006) Clinical diagnostic indicators of renal and bone damage in rats intramuscularly injected with depleted uranium. Radiat Prot Dosimetry 118:307-314. (National Institute of Radiological Sciences of Japan)
Abstract: The toxic effects and changes in biochemical markers related to kidney and bone in depleted uranium (DU)-injected rats were examined in order to clarify the relation between clinical biochemical markers and the degree of damage in these organs. Male Wistar rats received a single injection in the femoral muscles of 0.2, 1.0 or 2.0 mg kg^{-1} of DU which was dissolved in nitric acid solution adjusted to pH 3.2, for comparison with the group injected with nitric acid solution, and the control group. Urine and faeces were collected periodically over a 24 h period. Thereafter, the rats were killed at 28 d after DU injection. The body weights of the DU-injected groups decreased dose-dependently for the first 3-7 d, and then began to increase. The DU concentrations in the urine and faeces decreased rapidly within 3-7 d after DU injection. Urinary N-acetyl-ß-D-glucosaminidase (NAG)/creatinine peaked at the third day after DU injection, with a high correlation to the injected DU doses. There were high correlations among the injected DU doses, DU concentrations in the kidney and urinary NAG/creatinine values that were obtained at 28 d, respectively. The blood urea nitrogen (BUN) and creatinine in the serum also showed a high correlation with the DU-injected doses. The results indicated that urinary NAG/creatinine, BUN and creatinine in serum were useful indicators to diagnose the renal damage by DU, as well as to estimate the DU intake and concentration in the kidney when the intake is >2 mg kg^{-1} DU. The total bone mineral density of the proximal metaphysis of the tibia decreased in the 2 mg kg^{-1} DU group. In addition, alterations of the trabecular bone structure by inhibiting bone formation and promoting bone resorption were observed by bone histomorphometery. The bone biochemical markers osteocalcin, tartrate-resistance acid phosphatase, pyridinoline and rat-parathyroid hormone increased in all the DU injected groups, indicating that these markers were useful as sensitive indicators for diagnosing bone damage, even if the DU dose injected is low.

Gackstetter GD, Hooper TI, DeBakey SF, Johnson A, Nagaraj BE, Heller JM, Kang HK (2006) Fatal motor vehicle crashes among veterans of the 1991 Gulf War and exposure to munitions demolitions at Khamisiyah: a nested case-control study. Am J Ind Med 49:261-270. (DoD-102)
Abstract: BACKGROUND: A proposed explanation for the observed higher risk of fatal motor vehicle crashes (MVC) among 1991 Gulf War-deployed veterans is neurocognitive deficits resulting from nerve agent exposure at Khamisiyah, Iraq. Our objective was to assess any association between postwar fatal MVC and possible nerve agent exposure based on 2000 modeled plume data. METHODS: Cases were defined as MVC deaths with a record in the Department of Transportation Fatality Analysis Reporting System through 1995. Cases (n = 282) and controls (n = 3,131) were derived from a larger nested case-control study of Gulf War-era veterans and limited to Army, male, deployed personnel. Exposure and cumulative dose by case-control status were analyzed using multivariate techniques. RESULTS: Exposure status was not associated with fatal MVC (OR 0.96, 95% CI 0.72-1.26), nor were tertiles of cumulative dose. CONCLUSIONS: Findings do not support an association between possible exposures at Khamisiyah and postwar fatal MVC among Gulf War veterans.

Gamez W, Watson D, Doebbeling BN (2006) Abnormal personality and the mood and anxiety disorders: Implications for structural models of anxiety and depression. J Anxiety Disord. (DoD-058 and HHS-001)
Abstract: Substantial overlap exists between the mood and anxiety disorders. Previous research has suggested that their comorbidity can be explained by a shared factor (negative emotionality), but that they may also be distinguished by other unique components. The current study explicated these relations using an abnormal personality framework. Current diagnoses of major depression and several anxiety disorders were assessed in 563 Gulf War veterans. Participants also completed the schedule for nonadaptive and adaptive personality (SNAP) to determine how these disorders relate to abnormal personality traits. Analyses of individual diagnoses indicated that depression, generalized anxiety disorder (GAD), and post-traumatic stress disorder (PTSD) were more strongly related to personality than were other anxiety disorders. The Self-Harm Scale distinguished major depression from all other disorders, highlighting its significance for future structural models. Our results add to a growing body of evidence suggesting that GAD and PTSD have more in common with major depression than with their anxiety disorder counterparts.

Gendreau RM, Thorn MD, Gendreau JF, Kranzler JD, Ribeiro S, Gracely RH, Williams DA, Mease PJ, McLean SA, Clauw DJ (2005) Efficacy of milnacipran in patients with fibromyalgia. J Rheumatol 32:1975-1985.
Abstract: OBJECTIVE: Fibromyalgia (FM) is a common musculoskeletal condition characterized by widespread pain, tenderness, and a variety of other somatic symptoms. Current treatments are modestly effective. Arguably, the best studied and most effective compounds are tricyclic antidepressants (TCA). Milnacipran, a nontricyclic compound that inhibits the reuptake of both serotonin and norepinephrine, may provide many of the beneficial effects of TCA with a superior side effect profile. METHODS: One hundred twenty-five patients with FM were randomly assigned in a 3:3:2 ratio to receive milnacipran twice daily, milnacipran once daily, or placebo for 3 months in a double-blind dose-escalation trial; 92% of twice-daily and 81% of once-daily participants achieved dose escalation to the target milnacipran dose of 200 mg. RESULTS: The primary endpoint was reduction of pain. Both the once- and twice-daily groups showed statistically significant improvements in pain, as well as improvements in global well being, fatigue, and other domains. Response rates for patients receiving milnacipran were equal in patients with and without comorbid depression, but placebo response rates were considerably higher in depressed patients, leading to significantly greater overall efficacy in the nondepressed group. CONCLUSION: In this Phase II study, milnacipran led to statistically significant improvements in pain and other symptoms of FM. The effect sizes were equal to those previously found with TCA, and the drug was generally well tolerated.

Genovese RF, Benton BJ, Shippee SJ, Jakubowski EM, Bonnell JC (2006) Effects of low-level inhalation exposure to cyclosarin on learned behaviors in Sprague-Dawley rats. J Toxicol Environ Health A 69:2167-2180. (Funded by DoD)
Abstract: Behavioral and biochemical effects of low-level whole-body inhalation exposure to the chemical warfare nerve agent cyclosarin (GF) were evaluated. Sprague-Dawley rats were first trained on a variable-interval, 56-s (VI56) schedule of food reinforcement. The VI56 schedule specifies that a single lever press, following an average interval of 56 s, produces food reinforcement (i.e., a single food pellet). Subjects were then exposed to GF vapor at concentrations of 1.6-5.2 mg/m^3, or air control, for 60 min. Following exposures, performance on the VI56 and acquisition and maintenance of a radial-arm maze (RAM) spatial memory task were evaluated during 55 test sessions over approximately 11 wk. GF exposures produced miosis in all subjects and other mild clinical signs of

toxicity at the highest concentration. Convulsions were not observed in any subjects. GF exposures produced concentration-dependent decreases in acetylcholinesterase and butyrylcholinesterase activity. Additionally, blood assays revealed concentration-dependent levels of regenerated GF, thus verifying systemic exposure. The largest concentration of GF disrupted performance on the VI56 task. The deficit, however, resolved by the third postexposure test session. All subjects acquired, and maintained, performance on the RAM task, and no significant differences were seen as a result of GF exposure. No delayed effects from exposures were observed. These results demonstrate that, in rats, inhalation exposure to GF at levels below those producing convulsions and other severe clinical signs of toxicity may produce performance deficits on learned behaviors, but the deficits appear to not be persistent.

Genovese RF, Oubre JL, Jakubowski EM, Fleming PJ, Saxena A, Rockwood GA, Tipparaju P, Willmore CB (2006) Evaluation of cognitive and biochemical effects of low-level exposure to sarin in rhesus and African green monkeys. Toxicology 231:11-20.
Abstract: We investigated the potential of low-level exposures to the chemical warfare nerve agent, sarin, to produce adverse effects. Rhesus (Macaca mulatta) and African green monkeys (Chlorocebus acthiops) were trained on a serial probe recognition (SPR) task before IM administration of a low-level concentration (5.87mµg/kg or 2.93mµg/kg) of sarin. Blood was sampled before agent administration and at various times following administration. Sarin administration did not disrupt performance on the SPR task in either species. Major dependent measures characterizing performance (accuracy, number of completed trials per session, average choice response time) were largely unaffected on the day sarin was administered as well as on subsequent testing sessions occurring over several weeks following administration. Analyses of red blood cell (RBC) and plasma samples revealed that sarin administration produced a substantial degree of inhibition of circulating acetylcholinesterase (AChE) in RBC fractions and butyrylcholinesterase (BChE) in plasma fractions, which only slowly recovered. In this regard, AChE activity was inhibited to a greater extent than BChE activity. Blood samples were also evaluated for regenerated sarin, which was found in RBC and plasma fractions in both species and showed orderly elimination functions. More sarin was regenerated from RBC fractions than from plasma fractions. Elimination of regenerated sarin was much slower in RBC than plasma and exceeded the expected time of AChE aging, suggesting the presence of additional sarin binding sites. In general, effects were similar in both species. Taken together, our results show that while the concentrations of sarin administered were clearly biochemically active, they were below those that are required to produce a disruption of behavioral performance.

Gifford RK, Ursano RJ, Stuart JA, Engel CC (2006) Stress and stressors of the early phases of the Persian Gulf War. Philos Trans R Soc Lond B Biol Sci 361:585-591.
Abstract: Soldiers who deployed to Saudi Arabia in support of Operation Desert Shield were exposed to a wide variety of stressors. These stressors from the pre-combat phase of the deployment undoubtedly affect the current health of Gulf War veterans, but the exact mechanisms and linkages are not known. This article examines the nature of those stressors and possible effects on later health of veterans.

Glass DC, Sim MR (2006) The challenges of exposure assessment in health studies of Gulf War veterans. Philos Trans R Soc Lond B Biol Sci 361:627-637.
Abstract: A variety of exposures have been investigated in Gulf War veterans' health studies. These have most commonly been by self-report in a postal questionnaire but modelling and bio-monitoring have also been employed. Exposure assessment is difficult to do well in studies of any workplace environment. It is made more difficult in Gulf War studies where there are a number and variety of possible exposures, no agreed metrics for individual exposures and few contemporary records associating the exposure with an individual. In some studies, the exposure assessment was carried out some years after the war and in the context of media interest. Several studies have examined different ways to test the accuracy of exposure reporting in Gulf War cohorts. There is some evidence from Gulf War studies that self-reported exposures were subject to recall bias but it is difficult to assess the extent. Occupational exposure-assessment methodology can provide insights into the exposure-assessment process and how to do it well. This is discussed in the context of the Gulf War studies. Alternative exposure-assessment methodologies are presented, although these may not be suitable for widespread use in veteran studies. Due to the poor quality of and accessibility of objective military exposure records, self-assessed exposure questionnaires are likely to remain the main instrument for assessing the exposure for a large number of veterans. If this is to be the case, then validation methods with more objective methods need to be included in future study designs.

Glass DC, Sim MR, Kelsall HL, Ikin JF, McKenzie D, Forbes A, Ittak P (2006) What was different about exposures reported by male Australian Gulf War veterans for the 1991 Persian Gulf War, compared with exposures reported for other deployments? Mil Med 171:632-638. (Funded by Australian Government-Department of Veterans' Affairs)
Abstract: This study identified chemical and environmental exposures specifically associated with the 1991 Persian Gulf War. Exposures were self-reported in a postal questionnaire, in the period of 2000-2002, by 1,424 Australian male Persian Gulf War veterans in relation to their 1991 Persian Gulf War deployment and by 625 Persian Gulf War veterans and 514 members of a military comparison group in relation to other active deployments. Six of 28 investigated exposures were experienced more frequently during the Persian Gulf War than during other deployments; these were exposure to smoke (odds ratio [OR], 4.4; 95% confidence interval, 3.0-6.6), exposure to dust (OR, 3.7; 95% confidence interval, 2.6-5.3), exposure to chemical warfare agents (OR, 3.9; 95% confidence interval, 2.1-7.9), use of respiratory protective equipment (OR, 13.6; 95% confidence interval, 7.6-26.8), use of nuclear, chemical, and biological protective suits (OR, 8.9; 95% confidence interval, 5.4-15.4), and entering/inspecting enemy equipment (OR, 3.1; 95% confidence interval, 2.1-4.8). Other chemical and environmental exposures were not specific to the Persian Gulf War deployment but were also reported in relation to other deployments. The number of exposures reported was related to service type and number of deployments but not to age or rank.

Goldman M, Yaari A, Doshnitzki Z, Cohen-Luria R, Moran A (2006) Nephrotoxicity of uranyl acetate: effect on rat kidney brush border membrane vesicles. Arch Toxicol 80:387-393.
Abstract: Since the Gulf war exposure to depleted uranium, a known nephrotoxic agent, there is a renewed interest in the toxic effects of uranium in general and its mechanism of nephrotoxicity which is still largely unknown in particular. In order to investigate the mechanism responsible for uranium nephrotoxicity and the therapeutic effect of urine alkalization, we utilized rat renal brush border membrane vesicles (BBMV). Uranyl acetate (UA) caused a decrease in glucose transport in BBMV. The apparent K_i of uranyl was 139+/-30 µg uranyl/mg protein of BBMV. Uranyl at 140 µg/mg protein of BBMV reduced the maximal capacity of the system to transport glucose [V_{max} 2.2+/-0.2 and 0.96+/-0.16 nmol/mg protein for control and uranyl treated BBMV ($P<0.001$), respectively] with no effect on the apparent K_m (1.54+/-0.33 and 1.54+/-0.51 mM for control, and uranyl treated BBMV, respectively). This reduction in V_{max} is at least partially due to a decrease in the number of sodium-coupled glucose transporters as apparent from the reduction in phlorizin binding to the uranyl treated membranes, V_{max} was reduced from 247+/-13 pmol/mg protein in control BBMV to 119+/-3 pmol/mg protein in treated vesicles ($P<0.001$). The pH of the medium has a profound effect on the toxicity of UA on sodium-coupled glucose transport in BBMV: higher toxicity at neutral pH (around pH 7.0), and practically no toxicity at alkaline pH (7.6). This is the first report showing a direct inhibitory dose and pH dependent effect of uranyl on the glucose transport system in isolated apical membrane from kidney cortex

Golier JA, Legge J, Yehuda R (2006) The ACTH response to dexamethasone in Persian Gulf War veterans. Ann N Y Acad Sci 1071:448-453. (DoD-084)
Abstract: The basis of postdeployment health symptoms in Gulf War veterans remains poorly understood. Alterations in the feedback regulation of the hypothalamic-pituitary-adrenal (HPA) axis have been demonstrated in posttraumatic stress disorder (PTSD) and other bodily disorders related to stress. The objective of this article was to examine whether similar HPA axis alterations are related to Gulf War deployment, postdeployment health symptoms, or PTSD. Plasma adrenocorticotropic hormone (ACTH) was measured on consecutive mornings at 08:00 h before and after a low dose of oral dexamethasone (DEX) at 23:00 h in Gulf War veterans with PTSD (n = 14), Gulf War veterans without PTSD (n = 11), and healthy veterans never deployed to a war zone (n = 12). Both Gulf War veterans with PTSD and Gulf War veterans without PTSD had significantly lower post-DEX ACTH levels than the nonexposed veterans, in the absence of group differences in basal ACTH or DEX levels. Among Gulf War veterans, post-DEX ACTH levels were significantly associated with musculoskeletal symptoms. Gulf War deployment and postdeployment health symptoms appear to be associated with alterations in feedback regulation of the pituitary gland that suggests a possible common link between postdeployment health symptoms and other chronic stress-related conditions.

Golier JA, Schmeidler J, Legge J, Yehuda R (2006) Enhanced cortisol suppression to dexamethasone associated with Gulf War deployment. Psychoneuroendocrinology 31:1181-1189. (DoD-084)
Abstract: OBJECTIVE: To examine whether PTSD or post-deployment health symptoms in veterans of the first Gulf War (Operation Desert Shield/Storm) are associated with enhanced suppression of the pituitary-adrenal axis to

low-dose dexamethasone (DEX). METHOD: Plasma cortisol and lymphocyte glucocorticoid receptor (GR) number were measured at 08:00h on two consecutive days, before and after administration of 0.5mg of DEX at 23:00h in 42 male Gulf War veterans (14 without psychiatric illness, 16 with PTSD only, and 12 with both PTSD and MDD) and 12 healthy male veterans not deployed to the Gulf War or another war zone. RESULTS: In the absence of group differences in basal cortisol levels or GR number, Gulf War veterans without psychiatric illness and Gulf War veterans with PTSD only had significantly greater cortisol suppression to DEX than non-deployed veterans and Gulf War veterans with both PTSD and MDD. Gulf War deployment was associated with significantly greater cortisol suppression to DEX controlling for weight, smoking status, PTSD, and MDD; PTSD was not associated with response to DEX. Among Gulf War veterans musculoskeletal symptoms were significantly associated with cortisol suppression and those who reported taking anti-nerve gas pills (i.e., pyridostigmine bromide) during the war had significantly greater DEX-induced cortisol suppression than those who did not. CONCLUSIONS: The data demonstrate that alterations in neuroendocrine function are associated with deployment to the Gulf War and post-deployment musculoskeletal symptoms, but not PTSD. Additional studies are needed to examine the relationship of enhanced glucocorticoid responsivity to deployment exposures and chronic unexplained medical symptoms in Gulf War veterans.

Gray GC, Kang HK (2006) Healthcare utilization and mortality among veterans of the Gulf War. Philos Trans R Soc Lond B Biol Sci 361:553-569.
Abstract: The authors conducted an extensive search for published works concerning healthcare utilization and mortality among Gulf War veterans of the Coalition forces who served during the 1990-1991 Gulf War. Reports concerning the health experience of US, UK, Canadian, Saudi and Australian veterans were reviewed. This report summarizes 15 years of observations and research in four categories: Gulf War veteran healthcare registry studies, hospitalization studies, outpatient studies and mortality studies. A total of 149728 (19.8%) of 756373 US, UK, Canadian and Australian Gulf War veterans received health registry evaluations revealing a vast number of symptoms and clinical conditions but no suggestion that a new unique illness was associated with service during the Gulf War. Additionally, no Gulf War exposure was uniquely implicated as a cause for post-war morbidity. Numerous large, controlled studies of US Gulf War veterans' hospitalizations, often involving more than a million veterans, have been conducted. They revealed an increased post-war risk for mental health diagnoses, multi-symptom conditions and musculoskeletal disorders. Again, these data failed to demonstrate that Gulf War veterans suffered from a unique Gulf War-related illness. The sparsely available ambulatory care reports documented that respiratory and gastrointestinal complaints were quite common during deployment. Using perhaps the most reliable data, controlled mortality studies have revealed that Gulf War veterans were at increased risk of injuries, especially those due to vehicular accidents. In general, healthcare utilization data are now exhausted. These findings have now been incorporated into preventive measures in support of current military forces. With a few diagnostic exceptions such as amyotrophic lateral sclerosis, mental disorders and cancer, it now seems time to cease examining Gulf War veteran morbidity and to direct future research efforts to preventing illness among current and future military personnel.

Griffiths GD, Hornby RJ, Jagger CP, Brown AP, Stoten A, Pearce PC, Scott L, Pritchard DI (2006) Development of methods to measure humoral immune responses against selected antigens in the common marmoset (Callithrix jacchus) and the effect of pyridostigmine bromide administration. Int Immunopharmacol 6:1755-1764. (Funded by UK Ministry of Defence)
Abstract: This methodological study was carried out in preparation for a major long term study, also reported in this volume, which was designed to investigate whether the combination of vaccines and pyridostigmine bromide (PB) could have been responsible for adverse signs and symptoms reported by a number of veterans of the 1990/1991 Gulf conflict. In this context, the marmoset has been used to model aspects of the human immune system. The purposes of this methodological study were to select appropriate immunochemical reagents to measure humoral responses induced in marmosets in response to selected health and hygiene and biological warfare vaccines and to initially assess the effects of PB on the responses recorded. Vaccines were administered at 1/5th of a human dose, and also investigated in combination with the nerve agent pretreatment compound PB. PB dosing was selected to induce an inhibition of erythrocyte acetylcholinesterase by 30%. In order to assess the functionality of the immune system, antibody responses to a neo-antigen (keyhole limpet haemocyanin--KLH), administered some 2 months following the completion of the vaccination schedule, were measured. The present study identified appropriate isotyping reporter reagents which cross-reacted with equivalent marmoset immunoglobulins. Robust antibody responses were identified against anthrax protective antigen (PA), whole cell pertussis vaccine and KLH, while

weaker responses were measured against cholera and typhoid vaccines. The killed whole cell plague vaccine induced a response which was at the limit of detection of the assay. Co-administered PB had no discernable effect on immunological responses in this study.

Gueguen Y, Souidi M, Baudelin C, Dudoignon N, Grison S, Dublineau I, Marquette C, Voisin P, Gourmelon P, Aigueperse J (2006) Short-term hepatic effects of depleted uranium on xenobiotic and bile acid metabolizing cytochrome P450 enzymes in the rat. Arch Toxicol 80:187-195. (Funded by French Government: Institute for Radiological Protection and Nuclear Safety)
Abstract: The toxicity of uranium has been demonstrated in different organs, including the kidneys, skeleton, central nervous system, and liver. However, few works have investigated the biological effects of uranium contamination on important metabolic function in the liver. In vivo studies were conducted to evaluate its effects on cytochrome P450 (CYP) enzymes involved in the metabolism of cholesterol and xenobiotics in the rat liver. The effects of depleted uranium (DU) contamination on Sprague-Dawley were measured at 1 and 3 days after exposure. Biochemical indicators characterizing liver and kidney functions were measured in the plasma. The DU affected bile acid CYP activity: 7a-hydroxycholesterol plasma level decreased by 52% at day 3 whereas microsomal CYP7A1 activity in the liver did not change significantly and mitochondrial CYP27A1 activity quintupled at day 1. Gene expression of the nuclear receptors related to lipid metabolism (FXR and LXR) also changed, while PPARalpha mRNA levels did not. The increased mRNA levels of the xenobiotic-metabolizing CYP3A enzyme at day 3 may be caused by feedback up-regulation due to the decreased CYP3A activity at day 1. CAR mRNA levels, which tripled on day 1, may be involved in this up-regulation, while mRNA levels of PXR did not change. These results indicate that high levels of depleted uranium, acting through modulation of the CYP enzymes and some of their nuclear receptors, affect the hepatic metabolism of bile acids and xenobiotics.

Hooper TI, DeBakey SF, Bellis KS, Kang HK, Cowan DN, Lincoln AE, Gackstetter GD (2006) Understanding the effect of deployment on the risk of fatal motor vehicle crashes: a nested case-control study of fatalities in Gulf War era veterans, 1991-1995. Accid Anal Prev 38:518-525. (DoD-102)
Abstract: Motor vehicle crashes (MVCs) are an important cause of morbidity and premature loss of life among military personnel during peacetime and particularly following combat. A nested case-control study of fatal MVC occurring between 1991 and 1995 was conducted in a cohort of Gulf War era veterans. Cases were validated MVC deaths in the Fatality Analysis Reporting System. Controls were selected using risk set sampling by gender and year of case ascertainment in a 10:1 ratio. Preliminary results, consistent with previous reports of increased fatal MVC risk among returning combat veterans, showed a crude odds ratio of 1.45 (95% confidence interval 1.27-1.65). Multivariable logistic regression modeling was used to identify important independent predictors, as well as to quantify the influence of deployment on a risk profile for fatal MVC. Because of significant interaction between deployment and inpatient diagnosis of substance abuse, the final model was stratified by deployment status. Results suggest that demographic, military, and behavioral characteristics of deployed healthy warriors are similar to the risk profile for fatal MVC. In addition to young, single, high school-educated, enlisted male personnel, those who served during times of ground combat, particularly in infantry, gun crews, or seamanship occupations, should be targeted for preventive interventions.

Hornby RJ, Pearce PC, Bowditch AP, Scott L, Griffiths GD (2006) Multiple vaccine and pyridostigmine bromide interactions in the common marmoset Callithrix jacchus: immunological and endocrinological effects. Int Immunopharmacol 6:1765-1779. (Funded by UK Ministry of Defence)
Abstract: Following active service during the 1990/1991 Gulf Conflict, a number of UK and US veterans presented with a diverse range of symptoms, collectively known as Gulf Veterans Illnesses (GVI). The administration of vaccines and/or the pretreatment against possible nerve agent poisoning, pyridostigmine bromide (PB), given to Armed Forces personnel during the Gulf Conflict has been implicated as a possible factor in the aetiology of these illnesses. The possibility that adverse health effects may result from the administration of these vaccines (anthrax, pertussis, plague, yellow fever, polio, typhoid, tetanus, hepatitis B, meningococcal meningitis and cholera) and/or PB, have been investigated over an eighteen month period, in a non-human primate model, the common marmoset. This study reports immunological indices, including leukocyte phenotypes, intracellular cytokines IFN-? and IL-4 and antibody responses against vaccine antigens. Using human isotyping reagents previously shown to cross react with marmoset immunoglobulins (ibid) it was shown that marmosets responded strongly against anthrax PA and pertussis and weakly against killed whole cell plague, cholera and typhoid. At the end of the study the immune response to a previously unseen T-cell dependent antigen, keyhole limpet haemocyanin (KLH), was examined in order to determine whether immune function had been compromised by the compounds administered. Statistically

equivalent, robust antibody responses were measured against KLH in all treatment groups indicating that the immune system had not been compromised by any of the treatments. In addition, urinary cortisol was measured at key points throughout the study as an index of physiological stress which may have been induced by the treatments. There were no effects of treatment on urinary cortisol secretion. With respect to the other immunological indices measured, there were no statistical differences between the treatment groups during the period of the study.

Jamil H, Nassar-McMillan SC, Salman WA, Tahar M, Jamil LH (2006) Iraqi Gulf War veteran refugees in the U.S.: PTSD and physical symptoms. Soc Work Health Care 43:85-98.
Abstract: Veterans of the Gulf War present various symptoms and maladies. Reports by governmental and private entities have yielded mixed results and have been fraught with criticisms of biased research design. The vast majority of these studies have focused on U.S. veterans, with a much smaller number focusing upon British veterans. Very few have examined Iraqi Gulf War veterans. Our study involves administering a health issues questionnaire to a sample of Iraqi Gulf War veteran refugees in the U.S. Results indicate relationships between Post-Traumatic Stress Disorder (PTSD) scores and health outcome measures of chronic fatigue, fibromyalgia, functional status, quality of life, and health care utilization in terms of frequency and level of intensity. Implications for further inquiry are presented.

Jerjes WK, Peters TJ, Taylor NF, Wood PJ, Wessely S, Cleare AJ (2006) Diurnal excretion of urinary cortisol, cortisone, and cortisol metabolites in chronic fatigue syndrome. J Psychosom Res 60:145-153.
Abstract: OBJECTIVE: The aim of this study was to obtain comprehensive information on basal hypothalamic-pituitary-adrenal (HPA) axis activity in chronic fatigue syndrome (CFS) patients who were not affected by medication or comorbid psychiatric disorder likely to influence the HPA axis. METHOD: Steroid analysis of urine collections from 0600 to 2100 h at 3-h intervals in CFS patients and in controls. RESULTS: Urinary free cortisol and cortisone concentrations showed a significant normal diurnal rhythm, but levels were lower across the cycle in CFS. In contrast, while urinary cortisol metabolites also showed a normal diurnal rhythm, levels were not significantly different between the CFS and controls at any time. Derived metabolite ratios were similar in both groups. CONCLUSION: This study provides further evidence for reduced basal HPA axis function in patients with CFS, based on lower free cortisol and cortisone levels, but this is not corroborated by cortisol metabolite data. The difference between these measures cannot be explained by an altered timing of the diurnal rhythm.

Jerjes WK, Taylor NF, Peters TJ, Wessely S, Cleare AJ (2006) Urinary cortisol and cortisol metabolite excretion in chronic fatigue syndrome. Psychosom Med 68:578-582.
Abstract: OBJECTIVES: Reduced basal hypothalamic-pituitary-adrenal (HPA) axis output in chronic fatigue syndrome (CFS) has been inferred from low cortisol levels in blood, saliva, and urine in some studies. Because > 95% of cortisol is metabolized before excretion, we assessed cortisol output by assay of both cortisol metabolites and free cortisol in 24-hour urine collections and also investigated sex differences in these between CFS and control groups. METHOD: We calculated total urinary cortisol metabolites (TCM) and cortisol metabolite ratios from individual steroid data in 40 patients (20 males and 20 females) with CFS who were free of medication or comorbid psychiatric disorder likely to influence the HPA axis. Results were compared with those of 40 healthy volunteers (20 males and 20 females) well matched for age and body mass index. Data for free cortisol was obtained on 28 of the patients and 27 of the controls. RESULTS: The mean of TCM and cortisol metabolite ratios was not significantly different between patients and controls for either sex ($p > .05$ for all parameters). Previously established sex differences were confirmed in our controls and were found to be similar in CFS for TCM and the ratios 11OH/11OXO, 5a/5ß THF, and 20OH/20OXO (see text) ($p < .005$, $p < .05$, $p < .05$, and $p < .005$, respectively). Urinary free cortisol values were numerically (but not statistically) lower in patients with CFS than controls, and correlated inversely with fatigue levels in patients. CONCLUSION: The finding of normal urinary cortisol metabolite excretion in patients with CFS is at variance with earlier reports that CFS is a hypocortisolemic state. If serum and saliva cortisol levels are lower in CFS, this would suggest that metabolic clearance of cortisol is faster in patients with CFS than controls. This study also demonstrates that sex differences must be taken into account when interpreting results in patients with CFS.

Kato K, Sullivan PF, Evengard B, Pedersen NL (2006) Chronic widespread pain and its comorbidities: a population-based study. Arch Intern Med 166:1649-1654.
Abstract: BACKGROUND: Chronic widespread pain (CWP), the cardinal symptom of fibromyalgia, is prevalent and co-occurs with numerous symptom-based conditions such as chronic fatigue syndrome, joint pain, headache, irritable bowel syndrome, and psychiatric disorders. Few studies have examined the comorbidities of CWP in the

general population. Furthermore, little is known about the importance of familial (genetic and family environmental) factors in the etiology of co-occurrence. METHODS: Data were obtained from 44 897 individuals in the Swedish Twin Registry via computer-assisted telephone interview from 1998 through 2002 (age >/=42 years; 73.2% response rate). Screening for CWP was based on the American College of Rheumatology criteria without clinical evaluation. Measures for comorbidities were based on standard criteria when available. Odds ratios (ORs) were calculated in case-control and co-twin control designs to assess the effect of familial confounding in the associations. RESULTS: Considerable co-occurrences were found in CWP cases for chronic fatigue (OR, 23.53; 95% confidence interval [CI], 19.67-28.16), joint pain (OR, 7.41; 95% CI, 6.70-8.21), depressive symptoms (OR, 5.26; 95% CI, 4.75-5.82), and irritable bowel syndrome (OR, 5.17; 95% CI, 4.55-5.88). In co-twin control analyses, ORs were no longer significant for psychiatric disorders, whereas they decreased but remained significant for most other comorbidities. No changes in ORs were observed for headache. CONCLUSIONS: Associations between CWP and most comorbidities are mediated by unmeasured genetic and family environmental factors in the general population. The extent of mediation via familial factors is likely to be disorder specific.

Kelsall H, Sim M, McKenzie D, Forbes A, Leder K, Glass D, Ikin J, McFarlane A (2006) Medically evaluated psychological and physical health of Australian Gulf War veterans with chronic fatigue. J Psychosom Res 60:575-584. (Funded by Australian Government - Department of Veterans' Affairs)
Abstract: OBJECTIVE: The aim of this study was to evaluate fatigue in Australian Gulf War veterans and a military comparison group according to the 1994 chronic fatigue syndrome (CFS) definition and investigate the relation with exposures. METHODS: Comprehensive medical, psychological and reported exposure assessments of 1,456 veterans and 1,588 comparison group in a cross-sectional study. RESULTS: More Gulf War veterans had fatigue at all levels than did the military comparison group. The findings may be at least partly explained as an "active-deployment effect." The odds ratios increased with increasing clinical evaluation of the nature of the fatigue, even after adjustment for current psychiatric disorders in addition to other possible confounding factors. CONCLUSION: Medically unexplained chronic fatigue was more common, but not more disabling, in veterans than in the comparison group, but veterans with unexplained chronic fatigue had poorer health than veterans without. Within both populations, CFS is uncommon and at a similar level to the general community.

Kurkjian KM, Mahmutovic AJ, Kellar KL, Haque R, Bern C, Secor WE (2006) Multiplex analysis of circulating cytokines in the sera of patients with different clinical forms of visceral leishmaniasis. Cytometry A 69:353-358.
Abstract: BACKGROUND: The clinical spectrum of visceral leishmaniasis (VL), a chronic intracellular parasitic disease, ranges from a subclinical, asymptomatic infection to severe clinical disease (kala-azar). In experimental leishmaniasis, mice that have a Th1 response to infection tend to have limited disease while a Th2 response is associated with disease progression. Humans with VL most often have mixed rather than polarized responses. However, most clinical studies have used methods that require a relatively large sample volume, thus limiting their scope. Measuring multiple cytokine levels in blood samples using a multiplexed microsphere assay (MMA) may be useful to further evaluate the Th1/Th2 paradigm in humans. METHODS: Bangladeshi individuals (n=120) living in an area endemic for VL were categorized into one of the five clinical categories. Sera from these individuals were measured for levels of IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12, IFN-?, and TNF-a by multiplexed microsphere cytokine immunoassay. RESULTS: Circulating IL-8, IL-10, and IL-12 differed significantly among the clinical groups. Persons with kala-azar demonstrated the highest median levels of IL-8 and IL-10 but lower median levels of IL-12. CONCLUSIONS: The MMA for cytokines is an extremely time-and sample-efficient method for characterizing circulating cytokine levels in visceral leishmaniasis patients.

Lincoln AE, Helmer DA, Schneiderman AI, Li M, Copeland HL, Prisco MK, Wallin MT, Kang HK, Natelson BH (2006) The war-related illness and injury study centers: a resource for deployment-related health concerns. Mil Med 171:577-585. (Funded by VA)
Abstract: Combat veterans often return from deployment having experienced a wide range of exposures, symptoms, and medical conditions. The Department of Veterans Affairs established war-related illness and injury study centers to serve combat veterans with unexplained illnesses. We report the exposures, clinical status, and utilization of 53 combat veterans who participated in the National Referral Program (NRP) from January 2002 until March 2004. Participants were primarily male (81%) and served in the Persian Gulf War (79%). Common diagnoses were chronic fatigue syndrome (n = 23, 43%), neurotic depression (n = 21, 40%), and post-traumatic stress disorder (n = 20, 38%). Self-reported exposures related to weaponry, disease prophylaxis, environmental hazards, stress, and poor

hygiene. A small increase in mean SF-36V mental component scores (2.8 points, p = 0.009) and use of rehabilitation therapies (1.6 additional visits, p = 0.018) followed the NRP referral. The small gain in mental function suggests that the NRP may benefit combat veterans with long and complex medical histories.

Lincoln AE, Hooper TI, Kang HK, DeBakey SF, Cowan DN, Gackstetter GD (2006) Motor vehicle fatalities among Gulf War era veterans: characteristics, mechanisms, and circumstances. Traffic Inj Prev 7:31-37. (DoD-102)

Abstract: OBJECTIVES: Our objective was to describe fatal motor vehicle crashes (MVC) among veterans of the 1991 Gulf War era and to compare the distribution of crash and individual characteristics between those deployed to the Gulf War (GWV) and those not deployed (NDV). METHODS: We compared individual characteristics, crash mechanisms, and crash circumstances between 765 GWV and 553 NDV who died from MVC within the first five years of the war, between May 1991 and December 1995. RESULTS: Overall, GWV and NDV who died from a MVC were more likely to be enlisted males (97%), 21-30 years old (72%), have a high school education or less (91%), drive a passenger car (52%), and not use restraints (60%). The overall annual rate of motor vehicle fatalities for GWV (23.6 per 100,000; 95% confidence interval: 21.9-25.3) was significantly greater than the rate for NDV (15.9, 95% CI: 14.6-17.3). GWV with the highest motor vehicle fatality rates include males (24.8, 95% CI: 23.0-26.6), 17-20 year olds (105.0, 95% CI: 78.2-138.1), and those not married (27.3, 95% CI: 25.1-30.1). Adjusting for differences in age distribution across GWV and NDV did not account for the difference in rates. Characteristics of MVC fatalities that were over-represented among GWV include serving as regular active duty (p = 0.001), having a high school education or less (p = 0.01), being involved in a single-vehicle crash (p = 0.008), and dying within the first hour following the crash (p = 0.004). Also, we identified a greater proportion of alcohol-related crashes among GWV during the late night and early morning hours. CONCLUSIONS: The highest rates of motor vehicle fatality among young, single males in the military mirror the experience of the general population. Further research is necessary to determine modifiable risk factors that can be targeted for specific interventions and whether the elevated late night alcohol-related crash rate among GWV is an effect of deployment or an inherent population bias among those selected for operational deployments.

Maes M, Mihaylova I, De RM (2006) Lower serum zinc in Chronic Fatigue Syndrome (CFS): relationships to immune dysfunctions and relevance for the oxidative stress status in CFS. J Affect Disord 90:141-147.

Abstract: The present study examines serum zinc concentrations in patients with chronic fatigue syndrome (CFS) versus normal volunteers. Serum zinc levels were determined by means of an atomic absorption method. We found that serum zinc was significantly lower in the CFS patients than in the normal controls. There was a trend toward a significant negative correlation between serum zinc and the severity of CFS and there was a significant and negative correlation between serum zinc and the subjective experience of infection. We found that serum zinc was significantly and negatively correlated to the increase in the alpha2 protein fraction and positively correlated to decreases in the expression of mitogen-induced CD69+ (a T cell activation marker) on CD3+ as well as CD3+CD8+ T cells. These results show that CFS is accompanied by a low serum zinc status and that the latter is related to signs of inflammation and defects in early T cell activation pathways. Since zinc is a strong anti-oxidant, the present results further support the findings that CFS is accompanied by increased oxidative stress. The results of these reports suggest that some patients with CFS should be treated with specific antioxidants, including zinc supplements.

Maes M, Mihaylova I, Leunis JC (2005) In chronic fatigue syndrome, the decreased levels of omega-3 poly-unsaturated fatty acids are related to lowered serum zinc and defects in T cell activation. Neuro Endocrinol Lett 26:745-751.

Abstract: There is now evidence that major depression is accompanied by decreased levels of omega-3 poly-unsaturated fatty acids (PUFA), such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). There is a strong comorbidity between major depression and chronic fatigue syndrome (CFS). The present study has been carried out in order to examine PUFA levels in CFS. In twenty-two CFS patients and 12 normal controls we measured serum PUFA levels using gas chromatography and mass spectrometry. We found that CFS was accompanied by increased levels of omega-6 PUFAs, i.e. linoleic acid and arachidonic acid (AA), and mono-unsaturated fatty acids (MUFAs), i.e. oleic acid. The EPA/AA and total omega-3/omega-6 ratios were significantly lower in CFS patients than in normal controls. The omega-3/omega-6 ratio was significantly and negatively correlated to the severity of illness and some items of the FibroFatigue scale, i.e. aches and pain, fatigue and failing memory. The severity of illness was significantly and positively correlated to linoleic and arachidonic acid, oleic acid, omega-9 fatty acids and one of the saturated fatty acids, i.e. palmitic acid. In CFS subjects, we found

significant positive correlations between the omega-3/omega-6 ratio and lowered serum zinc levels and the lowered mitogen-stimulated CD69 expression on CD3+, CD3+ CD4+, and CD3+ CD8+ T cells, which indicate defects in early T cell activation. The results of this study show that a decreased availability of omega-3 PUFAs plays a role in the pathophysiology of CFS and is related to the immune pathophysiology of CFS. The results suggest that patients with CFS should respond favourably to treatment with--amongst other things—omega-3 PUFAs, such as EPA and DHA.

Maher KJ, Klimas NG, Fletcher MA (2005) Chronic fatigue syndrome is associated with diminished intracellular perforin. Clin Exp Immunol 142:505-511.
Abstract: Chronic fatigue syndrome (CFS) is an illness characterized by unexplained and prolonged fatigue that is often accompanied by abnormalities of immune, endocrine and cognitive functions. Diminished natural killer cell cytotoxicity (NKCC) is a frequently reported finding. However, the molecular basis of this defect of in vitro cytotoxicity has not been described. Perforin is a protein found within intracellular granules of NK and cytotoxic T cells and is a key factor in the lytic processes mediated by these cells. Quantitative fluorescence flow cytometry was used to the intracellular perforin content in CFS subjects and healthy controls. A significant reduction in the NK cell associated perforin levels in samples from CFS patients, compared to healthy controls, was observed. There was also an indication of a reduced perforin level within the cytotoxic T cells of CFS subjects, providing the first evidence, to our knowledge, to suggest a T cell associated cytotoxic deficit in CFS. Because perforin is important in immune surveillance and homeostasis of the immune system, its deficiency may prove to be an important factor in the pathogenesis of CFS and its analysis may prove useful as a biomarker in the study of CFS.

Maher MJ, Rego SA, Asnis GM (2006) Sleep disturbances in patients with post-traumatic stress disorder: epidemiology, impact and approaches to management. CNS Drugs 20:567-590.
Abstract: Subjective reports of sleep disturbance indicate that 70-91% of patients with post-traumatic stress disorder (PTSD) have difficulty falling or staying asleep. Nightmares are reported by 19-71% of patients, depending on the severity of their PTSD and their exposure to physical aggression. Objective measures of sleep disturbance are inconsistent, with some studies that used these measures indicating poor sleep and others finding no differences compared with non-PTSD controls. Future research in this area may benefit from examining measures of instability in the microstructure of sleep. Additionally, recent findings suggest that sleep disordered breathing (SDB) and sleep movement disorders are more common in patients with PTSD than in the general population and that these disorders may contribute to the brief awakenings, insomnia and daytime fatigue in patients with PTSD. Overall, sleep problems have an impact on the development and symptom severity of PTSD and on the quality of life and functioning of patients. In terms of treatments, SSRIs are commonly used to treat PTSD, and evidence suggests that they have a small but significant positive effect on sleep disruption. Studies of serotonin-potentiating non-SSRIs suggest that nefazodone and trazodone lead to significant reductions in insomnia and nightmares, whereas cyproheptadine may exacerbate sleep problems in patients with PTSD. Prazosin, a centrally acting alpha1-adrenoceptor antagonist, has led to large reductions in nightmares and insomnia in small studies of patients with PTSD. Augmentation of SSRIs with olanzapine, an atypical antipsychotic, may be effective for treatment-resistant nightmares and insomnia, although adverse effects can be significant. Additional medications, including zolpidem, buspirone, gabapentin and mirtazapine, have been found to improve sleep in patients with PTSD. Large randomised, placebo-controlled trials are needed to confirm the above findings. In contrast, evidence suggests that benzodiazepines, TCAs and MAOIs are not useful for the treatment of PTSD-related sleep disorders and their adverse effect profiles make further studies unlikely. Cognitive behavioural interventions for sleep disruption in patients with PTSD include strategies targeting insomnia and imagery rehearsal therapy (IRT) for nightmares. One large randomised controlled trial of group IRT demonstrated significant reductions in nightmares and insomnia. Similarly, uncontrolled studies combining IRT and insomnia strategies have demonstrated good outcomes. Uncontrolled studies of continuous positive airway pressure for SDB in patients with PTSD show that this treatment led to significant decreases in nightmares, insomnia and PTSD symptoms. Controlled studies are needed to confirm these promising findings.

McDiarmid MA, Engelhardt SM, Oliver M, Gucer P, Wilson PD, Kane R, Kabat M, Kaup B, Anderson L, Hoover D, Brown L, Albertini RJ, Gudi R, Jacobson-Kram D, Thorne CD, Squibb KS (2006) Biological monitoring and surveillance results of Gulf War I veterans exposed to depleted uranium. Int Arch Occup Environ Health 79:11-21. (Funded by VA)
Abstract: OBJECTIVE: To relate medical surveillance outcomes to uranium biomonitoring results in a group of depleted uranium (DU)-exposed, Gulf War I veterans. METHODS: Thirty-two veterans of Gulf War I who were

victims of 'friendly fire' involving DU weapons, in whom exposure assessment can accurately be measured, had urine uranium concentrations determined using ICP-MS technology. Clinical laboratory parameters were measured and related to urine uranium concentrations. Data were examined by stratifying the cohort into a low U group, <0.10 mug/g creatinine versus a high U group, >/=0.10 mµg/g creatinine and assessing differences between groups. RESULTS: Over a decade after first exposure, soldiers possessing embedded DU fragments continue to excrete elevated concentrations of uranium in urine. No clinically significant uranium related health effects were observed in blood count, blood chemistries including renal markers, neuropsychological measures, and semen quality or genotoxicity measures. Markers of early changes in renal glomerular and tubular function were not statistically different between groups; however, genotoxicity measures continue to show subtle, mixed results. CONCLUSION: Persistent urine uranium elevations continue to be observed more than 12 years since first exposure. Despite this, renal and other clinical abnormalities were not observed, likely due to the 'relatively' low uranium burden in this cohort compared to historical uranium-exposed occupational groups. Continuing surveillance is indicated, however, due to the on-going nature of the exposure. These results are an important finding in light of the on-going controversy regarding health effects observed in soldiers of the Gulf War and other conflicts, whose uranium exposure assessment is unable to be accurately determined.

McKenzie DP, McFarlane AC, Creamer M, Ikin JF, Forbes AB, Kelsall HL, Clarke DM, Glass DC, Ittak P, Sim MR (2006) Hazardous or harmful alcohol use in Royal Australian Navy veterans of the 1991 Gulf War: identification of high risk subgroups. Addict Behav 31:1683-1694. (Funded by Australian Government-Department of Veterans' Affairs)
Abstract: Elevated alcohol use disorders have been observed in 1991 Gulf War veterans from a variety of countries. This study used a self-report instrument, the Alcohol Use Disorders Identification Test (AUDIT), to ascertain whether any subgroups of 1232 male Royal Australian Navy (RAN) Gulf War veterans were at higher risk of hazardous or harmful alcohol use. Recursive partitioning/classification and regression tree (CART) analysis, followed by logistic regression, found five subgroups among the veterans, with differing risks of AUDIT caseness. The highest risk subgroup comprised current smokers. The other two high risk groups both consisted of former or never smokers of lower rank who were (1) not married, or (2) married, with a current diagnosis of major depression. The above subgroups were over three times as likely to exhibit AUDIT caseness than those who were former or never smokers of higher rank. The findings have important implications for effective development of public health initiatives designed to encourage safe alcohol use among veterans.

Miller RN, Costigan DJ, Young HA, Kang HK, Dalager N, Mathes RW, Crawford HC, Page WF, Thaul S (2006) Patterns of health care seeking of Gulf War registry members prior to deployment. Mil Med 171:370-375. (DoD-117)
Abstract: Following the Gulf War (GW), large numbers of individuals reported illness that they attributed to exposures encountered during the GW deployment. In response, the Department of Veterans Affairs and the Department of Defense established programs and registries for the evaluation and documentation of GW-related illness. We obtained registrants' medical records, which contained information on outpatient encounters during the 1-year period before their GW deployment, to determine whether registrants with multisymptom illness (cases) have patterns of predeployment health care seeking that are different from those of well registrants (controls). We found that subjects had significantly more predeployment outpatient visits than controls, but this varied by type of visit. Although the number of certain types of predeployment outpatient visits is significantly associated with subsequent multisymptom illness, these associations will have limited predictive value. These findings increase our understanding of multisymptom illness, especially its chronic nature, and justify doing additional studies.

Monleau M, Blanchardon E, Claraz M, Paquet F, Chazel V (2006) The effect of repeated inhalation on the distribution of uranium in rats. J Toxicol Environ Health A 69:1629-1649.
Abstract: For the assessment of doses after inhalation of airborne uranium compounds by workers, the International Commission on Radiological Protection (ICRP) developed compartmental models that are used to calculate reference dose coefficients and retention and excretion functions. It is assumed that each acute intake has no effect on the biokinetics of later intakes. Consequently, retention and excretion after multiple or chronic exposure are predicted using the same models as after acute exposure. This assumption was tested here on rats exposed to repeated inhalation of uranium dioxide (UO_2). First, excretion and organ retention were determined after a single inhalation of UO_2. The follow-up of incorporated activity was used to design a biokinetic model for uranium inhaled by rats. Second, the biokinetics of uranium were monitored in two experiments of repeated inhalations of uranium dioxide under different intake patterns. For these two experiments, the organs' retention and excretion after repeated

UO_2 inhalation were predicted using the biokinetic model and compared to the experimental measurement. Under the two sets of experimental conditions considered, the prediction of the biokinetic model based on acute exposure data was consistent with the biokinetics observed after repeated UO_2 inhalations, with the possible exception of retention in the skeleton.

Monleau M, De MM, Frelon S, Paquet F, Donnadieu-Claraz M, Dumenil G, Chazel V (2006) Distribution and genotoxic effects after successive exposure to different uranium oxide particles inhaled by rats. Inhal Toxicol 18:885-894.
Abstract: In nuclear fuel cycle facilities, workers may inhale airborne uranium compounds that lead to internal contamination, with various exposure scenarios depending on the workplace. These exposures can be chronic, repeated, or acute, and can involve many different compounds. The effect of uranium after multiple scenarios of exposure is unknown. The aim of this study, therefore, was to investigate the genotoxic and biokinetics consequences of exposure to depleted insoluble uranium dioxide (UO_2) by repeated or acute inhalation on subsequent acute inhalation of moderately soluble uranium peroxide (UO_4) in rats. The results show that UO_2 repeated preexposure by inhalation increases the genotoxic effects of UO_4 inhalation, assessed by comet assay, in different cell types, when UO_4 exposure alone has no effect. At the same time, the study of UO4 bioaccumulation showed that the UO_4 biokinetics in the kidneys, gastrointestinal tract, and excreta, but not in the lungs, were slightly modified by previous UO_2 exposures. All these results show that both genotoxic and biokinetics effects of uranium may depend on preexposure and that repeated exposure induces a potentiation effect compared with acute exposure.

Monleau M, De MM, Paquet F, Chazel V, Dumenil G, Donnadieu-Claraz M (2006) Genotoxic and inflammatory effects of depleted uranium particles inhaled by rats. Toxicol Sci 89:287-295. (Funded by French Government: Institute for Radiological Protection and Nuclear Safety)
Abstract: Depleted uranium (DU) is a radioactive heavy metal coming from the nuclear industry and used in numerous military applications. Uranium inhalation can lead to the development of fibrosis and neoplasia in the lungs. As little is known concerning the molecular processes leading to these pathological effects, some of the events in terms of genotoxicity and inflammation were investigated in rats exposed to DU by inhalation. Our results show that exposure to DU by inhalation resulted in DNA strand breaks in broncho-alveolar lavage (BAL) cells and in increase of inflammatory cytokine expression and production of hydroperoxides in lung tissue suggesting that the DNA damage was in part a consequence of the inflammatory processes and oxidative stress. The effects seemed to be linked to the doses, were independent of the solubility of uranium compounds and correlating with the type of inhalation. Repeated inhalations seemed to induce an effect of potentiation in BAL cells and also in kidney cells. Comet assay in neutral conditions revealed that DNA damage in BAL cells was composed partly by double strands breaks suggesting that radiation could contribute to DU genotoxic effects in vivo. All these in vivo results contribute to a better understanding of the pathological effect of DU inhalation.

Monson CM, Schnurr PP, Resick PA, Friedman MJ, Young-Xu Y, Stevens SP (2006) Cognitive processing therapy for veterans with military-related posttraumatic stress disorder. J Consult Clin Psychol 74:898-907. (Funded by VA National Center for PTSD)
Abstract: Sixty veterans (54 men, 6 women) with chronic military-related posttraumatic stress disorder (PTSD) participated in a wait-list controlled trial of cognitive processing therapy (CPT). The overall dropout rate was 16.6% (20% from CPT, 13% from waiting list). Random regression analyses of the intention-to-treat sample revealed significant improvements in PTSD and comorbid symptoms in the CPT condition compared with the wait-list condition. Forty percent of the intention-to-treat sample receiving CPT did not meet criteria for a PTSD diagnosis, and 50% had a reliable change in their PTSD symptoms at posttreatment assessment. There was no relationship between PTSD disability status and outcomes. This trial provides some of the most encouraging results of PTSD treatment for veterans with chronic PTSD and supports increased use of cognitive- behavioral treatments in this population.

Mori DL, Sogg S, Guarino P, Skinner J, Williams D, Barkhuizen A, Engel C, Clauw D, Donta S, Peduzzi P (2006) Predictors of exercise compliance in individuals with Gulf War veterans' illnesses: Department of Veterans Affairs Cooperative Study 470. Mil Med 171:917-923. (VA-062 and DoD-115)
Abstract: Although the health benefits of exercise for individuals with Persian Gulf War veterans' illnesses (GWVI) are documented, many of these individuals do not exercise regularly enough to obtain benefits. The purpose of this study was to investigate factors predicting exercise compliance among individuals with GWVI in a multicenter, randomized, clinical trial. Participants were 1,092 veterans who reported at least two of the following cardinal

symptoms of GWVI: (1) fatigue, (2) musculoskeletal pain, and (3) cognitive problems. Participants received exercise alone or exercise and cognitive-behavioral therapy. The overall level of compliance was relatively low during the exercise treatment phase (46.2%) and decreased by one-half during the follow-up period (23.0%). Predictors of compliance during treatment included less pain and greater age, motivation, and body mass index. Predictors of compliance during the follow-up period included less pain and greater age. The results highlight factors that affect adoption and maintenance of physical activity in a population with GWVI.

Morris M, Key MP, Farah V (2007) Sarin produces delayed cardiac and central autonomic changes. Exp Neurol 203:110-115. (Funded by DoD)
Abstract: The aim was to evaluate the acute and delayed effects of low dose sarin exposure on cardiac autonomic and brainstem catecholaminergic function in mice. The rationale was to expand our knowledge of the cardiovascular effects of this neurotoxic, acetylcholinesterase (AChE) inhibitor. C57BL/6 male mice with telemetric arterial catheters were injected with saline or sarin (8 mμg/kg, 0.05x LD_{50}; sc, two injections) with blood pressure (BP) measurements made at 1 and 10 weeks after sarin exposure. BP and pulse interval variability (PI) and low and high frequency spectral oscillations were measured using autoregressive spectral analysis. In situ hybridization (ISH) was used to quantify tyrosine hydroxylase (TH) mRNA expression in brainstem cardiovascular centers. Sarin had no effect on blood AChE activity, heart rate (HR) or BP. There was a biphasic response in PI variance, an early increase (+140%) and a delayed decrease (-62%) at more than 2 months after sarin exposure. There were no changes in BP variance. Assuming that increased PI variance is a positive outcome, the short-term response to sarin should be protective. This is opposite for the delayed decrease in PI variance which is associated with adverse cardiovascular effects. There was an increase in TH mRNA in both locus coeruleus (0.18+/-0.05 vs. 1.4+/-0.2 muCi/g; control vs. sarin) and dorsal vagal complex (0.09+/-0.06 vs. 1.17+/-0.03 muCi/g; control vs. sarin). Results show that a dose of sarin which had no peripheral cholinergic effects caused changes in autonomic modulation, a short-term enhancement followed by a delayed impairment in heart rate variability. Sarin-induced cardiac effects suggest a controversial aspect to the use of pharmacological agents which target AChE for management of cardiovascular risk.

Murphy D, Hooper R, French C, Jones M, Rona R, Wessely S (2006) Is the increased reporting of symptomatic ill health in Gulf War veterans related to how one asks the question? J Psychosom Res 61:181-186. (Funded by UK Ministry of Defence)
Abstract: BACKGROUND: Following the 1991 Gulf War (GW) there was much controversy surrounding service-related health effects. Evidence from the Vietnam experience suggested that self-reported ill health following that conflict might be related to how service during the conflict is framed. The aim of this article is to determine if a GW health effect persisted when the same questions were asked in a "non-GW" context. METHOD: Prevalence of physical and psychological health problems were ascertained in a study assessing health screening from a random sample of UK Armed Forces. Record linkage between the screening survey and service history was conducted to obtain information on participation in the GW. RESULTS: Differences in health outcomes were found between the GW and the non-GW groups. This difference existed for symptomatic measures (OR=1.84, 95% CI, 1.17-2.91) rather than psychological or behavioral measures. No differences were found in psychological measures such as PTSD or behavioral measures such as alcohol consumption. Those deployed to the GW had a poorer self-perception of health (OR=1.47, 95% CI 1.02-2.11). CONCLUSIONS: Even in the absence of framing, a Gulf-related ill health effect was found.

Muse WT, Thomson S, Crouse C, Matson K (2006) Generation, sampling, and analysis for low-level GB (Sarin) and GF (Cyclosarin) vapor for inhalation toxicology studies. Inhal Toxicol 18:1101-1108. (Funded by DoD)
Abstract: This study tested and optimized various methodologies to generate, sample, and characterize GB and GF test atmospheres in an inhalation chamber, particularly at low vapor levels. A syringe drive/spray atomization system produced vapor concentrations at a range of 1-50 mg/m^3. A saturator cell was used to generate vapor at sub-lethal concentrations ranging from 1 mg/m^3 down to low levels approaching the threshold limit value time-weighted average (TLV-TWA) of 0.0001 mg/m^3 for GB. Both generation techniques demonstrated the ability to produce stable vapor concentrations over extended exposure periods. This capability was important to determine sublethal nerve agent effects, such as miosis, for inhalation toxicology studies. In addition, the techniques employed for producing and maintaining low-level agent vapor would lay the foundation for testing less volatile chemical warfare agents such as VX.

Olgun S, Misra HP (2006) Pesticides induced oxidative stress in thymocytes. Mol Cell Biochem 290:137-144.
Abstract: The role of oxidative stress in immune cell toxicity caused by the pesticides lindane, malathion and permethrin was investigated in thymic cells from C57BL/6 mice. Thymocytes treated with any of these pesticides (concentrations ranging between 50-150 µM) were found to generate both superoxide ($^{*}O_2^-$) and H_2O_2. The production of $^{*}O_2^-$ was detected with hydroethidine-ethidium bromide assay. H_2O_2 production was monitored with a flow cytometric fluorescent (DCFH-DA) assay. All three pesticides stimulated $^{*}O_2^-$ release after 5 min exposure. Lindane and permethrin, but not malathion, continued to have significant ($p < or = 0.05$) effects on $^{*}O_2^-$ generation following 15 min of exposure. The lindane + malathion mixture was found to cause more-than-additive increase in $^{*}O_2^-$ production compared to individual pesticide treatments (at both 5 and 15 min). However, the effect of the lindane + permethrin mixture was not significantly different than individual components of this mixture. The effects of these pesticides on levels of antioxidant enzymes were also investigated, and only mixtures were found to have significant ($p < or = 0.05$) effects. Thus, lindane + malathion and lindane + permethrin mixtures increased total superoxide dismutase (SOD) specific activity, had no effect on catalase levels and inhibited GSH-peroxidase and GSH-reductase specific activities. Although the results of these studies do not explain the mechanism of action of these pesticides on the generation of $^{*}O_2^-$ and H_2O_2, it is worthy of note that mixtures of these chemicals have oxidative responses greater than those of single chemicals.

Ough EA, Lewis BJ, Andrews WS, Bennett LG, Hancock RG, D'Agastino PA (2006) Determination of natural and depleted uranium in urine at the ppt level: an interlaboratory analytical exercise. Health Phys 90:494-499. (Funded by Canadian Department of National Defence)
Abstract: An analytical exercise was initiated in order to determine those procedures with the capability to measure total uranium and uranium ($^{238}U/^{235}U$) isotopic ratios in urine samples containing >0.02 µg U kg^{-1} urine. A host laboratory prepared six identical sets of twelve synthetic urine samples containing total uranium in the range of 25 to 770 ng U kg^{-1} urine and with $^{238}U/^{235}U$ isotopic ratios ranging from 138 (100% NU) to 215 (51% DU). Sets of samples were shipped to five testing laboratories (four based in Canada and one based in Europe). Each laboratory utilized one of the following analytical techniques: sector field inductively coupled plasma mass spectrometry (ICP-SF-MS), quadrupole inductively coupled plasma mass spectrometry (ICP-Q-MS), thermal ionization mass spectrometry (TIMS), and instrumental/delayed neutron activation analysis (I/DNAA), in their analyses.

Ozakinci G, Hallman WK, Kipen HM (2006) Persistence of symptoms in veterans of the First Gulf War: 5-year follow-up. Environ Health Perspect 114:1553-1557. (VA-005A, HHS-006)
Abstract: BACKGROUND: During the 1990-1991 Gulf War, approximately 700,000 U.S. troops were deployed to the Persian Gulf theater of operations. Of that number, approximately 100,000 have presented medical complaints through various registry and examination programs. OBJECTIVES: Widespread symptomatic illness without defining physical features has been reported among veterans of the 1991 Gulf War. We ascertained changes in symptom status between an initial 1995 symptom evaluation and a follow-up in 2000. METHODS: We assessed mailed symptom survey questionnaires for 390 previously surveyed members of the U.S. Department of Veterans Affairs Gulf War Registry for changes over the 5-year interval in terms of number and severity of symptoms. RESULTS: For the cohort as a whole, we found no significant changes in symptom number or severity. Those initially more symptomatic in 1995 showed some improvement over time, but remained much more highly symptomatic than those who had lesser initial symptomatology. CONCLUSIONS: The symptom outbreak following the 1991 Gulf War has not abated over time in registry veterans, suggesting substantial need for better understanding and care for these veterans.

Paquet F, Houpert P, Blanchardon E, Delissen O, Maubert C, Dhieux B, Moreels AM, Frelon S, Gourmelon P (2006) Accumulation and distribution of uranium in rats after chronic exposure by ingestion. Health Phys 90:139-147. (Funded by French Government: Institute for Radiological protection and Nuclear Safety)
Abstract: Data describing the biokinetics of radionuclides after contamination come mainly from experimental acute exposures of laboratory animals and follow-up of incidental exposures of humans. These data were compiled to form reference models that could be used for dose calculation in humans. In case of protracted exposure, the same models are applied, assuming that they are not modified by the duration of exposure. This work aims at testing this hypothesis. It presents new experimental data on retention of uranium after chronic intake, which are compared to values calculated from a biokinetic model that is based on experiments of acute exposure of rats to uranium. Experiments were performed with 56 male Sprague Dawley rats, from which 35 were exposed during their whole adult life to 40 mg L of uranyl nitrate dissolved in mineral water and 21 were kept as controls. Animals were euthanatized at 32, 95, 186, 312, 368, and 570 d after the beginning of contamination. Urine and all tissues were

removed, weighted, mineralized, and then analyzed for uranium content by Kinetics Phosphorescence Analysis (KPA) or by ICP-MS. Experimental data showed that uranium accumulated in most organs, following a nonmonotonous pattern. Peaks of activities were observed at 1-3, 10, and 19 mo after the beginning of exposure. Additionally, accumulation was shown to occur in tissues such as teeth and brain that are not usually described as target organs. Comparison with model prediction showed that the accumulation of uranium in target organs after chronic exposure is overestimated by the use of a model designed for acute exposure. These differences indicate that protracted exposure to uranium may induce changes in biokinetic parameters when compared to acute contamination and that calculation of dose resulting from chronic intake of radionuclides may need specific models that are not currently available.

Parrish RR, Thirlwall MF, Pickford C, Horstwood M, Gerdes A, Anderson J, Coggon D (2006) Determination of 238u/235u, 236u/238u and uranium concentration in urine using sf-icp-ms and mc-icp-ms: an interlaboratory comparison. Health Phys 90:127-138. (British study)
Abstract: Accidental exposure to depleted or enriched uranium may occur in a variety of circumstances. There is a need to quantify such exposure, with the possibility that the testing may post-date exposure by months or years. Therefore, it is important to develop a very sensitive test to measure precisely the isotopic composition of uranium in urine at low levels of concentration. The results of an interlaboratory comparison using sector field (SF)-inductively coupled plasma-mass spectrometry (ICP-MS) and multiple collector (MC)-ICP-MS for the measurement of uranium concentration and $^{235}U/^{238}U$ and $^{236}U/^{238}U$ isotopic ratios of human urine samples are presented. Three urine samples were verified to contain uranium at 1-5 ng L^{-1} and shown to have natural uranium isotopic composition. Portions of these urine batches were doped with depleted uranium (DU) containing small quantities of ^{236}U, and the solutions were split into 100 mL and 400 mL aliquots that were subsequently measured blind by three laboratories. All methods investigated were able to measure accurately $^{238}U/^{235}U$ with precisions of ~ 0.5% to ~ 4%, but only selected MC-ICP-MS methods were capable of consistently analyzing $^{236}U/^{238}U$ to reasonable precision at the ~ 20 fg L^{-1} level of ^{236}U abundance. Isotope dilution using a ^{233}U tracer demonstrates the ability to measure concentrations to better than +/-4% with the MC-ICP-MS method, though sample heterogeneity in urine samples was shown to be problematic in some cases. MC-ICP-MS outperformed SF-ICP-MS methods, as was expected. The MC-ICP-MS methodology described is capable of measuring to ~ 1% precision the $^{238}U/^{235}U$ of any sample of human urine over the entire range of uranium abundance down to <1 ng L^{-1}, and detecting very small amounts of DU contained therein.

Pasinetti GM, Ungar LH, Lange DJ, Yemul S, Deng H, Yuan X, Brown RH, Cudkowicz ME, Newhall K, Peskind E, Marcus S, Ho L (2006) Identification of potential CSF biomarkers in ALS. Neurology 66:1218-1222.
Abstract: BACKGROUND: The clinical diagnosis of ALS is based entirely on clinical features. Identification of biomarkers for ALS would be important for diagnosis and might also provide clues to pathogenesis. OBJECTIVE: To determine if there is a specific protein profile in the CSF that distinguishes patients with ALS from those with purely motor peripheral neuropathy (PN) and healthy control subjects. METHODS: CSF obtained from patients with ALS, disease controls (patients with other neurologic disorders), and normal controls were analyzed using the surface-enhanced laser desorption/ionization time-of-flight mass spectrometry proteomics technique. Biomarker sensitivity and specificity was calculated with receiver operating characteristic curve methodology. ALS biomarkers were purified and sequence identified by mass spectrometry-directed peptide sequencing. RESULTS: In initial proteomic discovery studies, three protein species (4.8-, 6.7-, and 13.4-kDa) that were significantly lower in concentration in the CSF from patients with ALS (n = 36) than in normal controls (n = 21) were identified. A combination of three protein species (the "three-protein" model) correctly identified patients with ALS with 95% accuracy, 91% sensitivity, and 97% specificity from the controls. Independent validation studies using separate cohorts of ALS (n = 13), healthy control (n = 25), and PN (n = 7) subjects confirmed the ability of the three CSF protein species to separate patients with ALS from other diseases. Protein sequence analysis identified the 13.4-kDa protein species as cystatin C and the 4.8-kDa protein species as a peptic fragment of the neurosecretory protein VGF. CONCLUSION: Additional application of a "three-protein" biomarker model to current diagnostic criteria may provide an objective biomarker pattern to help identify patients with ALS.

Peakman M, Skowera A, Hotopf M (2006) Immunological dysfunction, vaccination and Gulf War illness. Philos Trans R Soc Lond B Biol Sci 361:681-687.
Abstract: One candidate cause of Gulf War illness is vaccination against infectious diseases including medical counter-measures against biological weapons. One influential theory has suggested that such mass-vaccination

caused a shift in immune response to a Type 2 cytokine pattern (Th2), which it was suggested was accompanied by a chronic fatigue syndrome-like illness. This article critically appraises this theory. We start by examining epidemiological evidence, which indicates that single vaccines are unlikely to be a substantial cause of Gulf War illness, but that there was a modest relationship with multiple vaccines, which was strongest in those vaccinated while deployed to the Gulf. These relationships may be affected by recall bias. We conclude by examining the results of immunological studies carried out in veterans or in a relevant setting in vitro. The balance of evidence from immunological studies on veterans returning from the War, including those developing multi-symptom illness, is that the immune response has not become polarized towards Th2. In summary, the epidemiological evidence for a multiple vaccine effect on Gulf War-related illness remains a potentially important aetiological lead, but mechanistic studies available at this stage do not identify any immunological basis for it.

Pourahmad J, Ghashang M, Ettehadi HA, Ghalandari R (2006) A search for cellular and molecular mechanisms involved in depleted uranium (DU) toxicity. Environ Toxicol 21:349-354.
Abstract: Addition of U(VI) (uranyl acetate) to isolated rat hepatocytes results in rapid glutathione oxidation, reactive oxygen species (ROS) formation, lipid peroxidation, decreased mitochondrial membrane potential, and lysosomal membrane rupture before hepatocyte lysis occurred. Cytotoxicity was prevented by ROS scavengers, antioxidants, and glutamine (ATP generator). Hepatocyte dichlorofluorescein oxidation was inhibited by mannitol (a hydroxyl radical scavenger) or butylated hydroxyanisole and butylated hydroxytoluene (antioxidants). Glutathione depleted hepatocytes were resistant to U(VI) toxicity and much less dichlorofluorescein oxidation occurred. Reduction of U(VI) by glutathione or cysteine in vitro was also accompanied by oxygen uptake and was inhibited by Ca(II) (a U(IV) or U(VI) reduction inhibitor). U(VI)-induced cytotoxicity and ROS formation was also inhibited by Ca(II), which suggests that U(IV) and U(IV) GSH mediate ROS formation in isolated hepatocytes. The U(VI) reductive mechanism required for toxicity has not been investigated. Cytotoxicity was also prevented by cytochrome P450 inhibitors, particularly CYP 2E1 inhibitors, but not inhibitors of DT diaphorase or glutathione reductase. This suggests that P450 reductase and reduced cytochrome P450 contributes to U(VI) reduction to U(IV). In conclusion, U(VI) cytotoxicity is associated with mitochondrial/lysosomal toxicity by the reduced biological metabolites and ROS.

Proctor SP, Heaton KJ, Heeren T, White RF (2006) Effects of sarin and cyclosarin exposure during the 1991 Gulf War on neurobehavioral functioning in US army veterans. Neurotoxicology. (VA-004)
Abstract: BACKGROUND: During the Gulf War (GW), in early March 1991, a munitions dump at Khamisiyah, Iraq, was destroyed. Later, in 1996, the dump was found to have contained the organophosphate chemical warfare agents, sarin and cyclosarin. METHODS: Data collected in a study conducted between 1994 and 1996, before the Khamisiyah incident was publicly disclosed, were used to examine neurobehavioral task performances of GW veterans (n=140) categorized as having received high, moderate, or low-to-no exposure dose levels to sarin and cyclosarin at Khamisiyah, Iraq. Exposure levels were based on modeled estimates of the exposure plume and on troop location information at the time of the Khamisiyah event. Based on recent findings observed in follow-up studies of persons exposed to sarin during the 1995 terrorist attacks in Japan, we hypothesized that exposure to sarin and cyclosarin would be associated with poorer performances on objective neurobehavioral tasks in specific functional domains (particularly in visuospatial abilities and psychomotor functioning) in a dose-dependent manner. RESULTS: Sarin and cyclosarin exposure was significantly associated with less proficient neurobehavioral functioning on tasks involving fine psychomotor dexterity and visuospatial abilities 4-5 years after exposure. CONCLUSIONS: Findings suggest a dose-response association between low-level exposure to sarin and cyclosarin and specific functional central nervous system effects 4-5 years after exposure.

Rajeevan MS, Smith AK, Dimulescu I, Unger ER, Vernon SD, Heim C, Reeves WC (2006) Glucocorticoid receptor polymorphisms and haplotypes associated with chronic fatigue syndrome. Genes Brain Behav.
Abstract: Chronic fatigue syndrome (CFS) is a significant public health problem of unknown etiology, the pathophysiology has not been elucidated, and there are no characteristic physical signs or laboratory abnormalities. Some studies have indicated an association of CFS with deregulation of immune functions and hypothalamic-pituitary-adrenal (HPA) axis activity. In this study, we examined the association of sequence variations in the glucocorticoid receptor gene (NR3C1) with CFS because NR3C1 is a major effector of the HPA axis. There were 137 study participants (40 with CFS, 55 with insufficient symptoms or fatigue, termed as ISF, and 42 non-fatigued controls) who were clinically evaluated and identified from the general population of Wichita, KS. Nine single nucleotide polymorphisms (SNPs) in NR3C1 were tested for association of polymorphisms and haplotypes with CFS. We observed an association of multiple SNPs with chronic fatigue compared to non-fatigued (NF) subjects (P

< 0.05) and found similar associations with quantitative assessments of functional impairment (by the SF-36), with fatigue (by the Multidimensional Fatigue Inventory) and with symptoms (assessed by the Centers for Disease Control Symptom Inventory). Subjects homozygous for the major allele of all associated SNPs were at increased risk for CFS with odds ratios ranging from 2.61 (CI 1.05-6.45) to 3.00 (CI 1.12-8.05). Five SNPs, covering a region of approximately 80 kb, demonstrated high linkage disequilibrium (LD) in CFS, but LD gradually declined in ISF to NF subjects. Furthermore, haplotype analysis of the region in LD identified two associated haplotypes with opposite alleles: one protective and the other conferring risk of CFS. These results demonstrate NR3C1 as a potential mediator of chronic fatigue, and implicate variations in the 5' region of NR3C1 as a possible mechanism through which the alterations in HPA axis regulation and behavioural characteristics of CFS may manifest.

Rose MR, Brix KA (2006) Neurological disorders in Gulf War veterans. Philos Trans R Soc Lond B Biol Sci 361:605-618.
Abstract: We present a review of neurological function in Gulf War veterans (GWV). Twenty-two studies were reviewed, including large hospitalization and registry studies, large population-based epidemiological studies, investigations of a single military unit, small uncontrolled studies of ill veterans and small controlled studies of veterans. In nearly all studies, neurological function was normal in most GWVs, except for a small proportion who were diagnosed with compression neuropathies (carpal tunnel syndrome or ulnar neuropathy). In the great majority of controlled studies, there were no differences in the rates of neurological abnormalities in GWVs and controls. In a national US study, the incidence of amyotrophic lateral sclerosis (ALS) seems to be significantly increased in GWVs, compared to the rate in controls. However, it is possible that military service, in general, might be associated with an increased risk of ALS, rather than Gulf War service in particular. Taken together, the conclusion is that if a neurological examination in a GWV is within normal limits, then extensive neurological testing is unlikely to diagnose occult neurological disorders.

Roy MJ, Kraus PL, Cooper JA, Cherstniakova S, Coll R, Seegers CA, Deuster PA, Koslowe P, Law WA, Krantz DS, Cantilena L (2006) Initial evaluation of N,N-diethyl-m-toluamide and permethrin absorption in human volunteers under stress conditions. Mil Med 171:122-127. (DoD-124)
Abstract: OBJECTIVES: This was a pilot study to determine (1) whether it is feasible to effectively blind human subjects to the presence of the insect repellents N,N-diethyl-m-toluamide (DEET) and permethrin; (2) whether DEET affects the absorption of permethrin; and (3) whether combat videotape viewing and mental arithmetic are stressful. METHODS: Ten volunteers were exposed to DEET, permethrin, and stress (1-hour combat videotape plus mental arithmetic) in a double-blind, randomized, placebo-controlled trial. Outcome measurements included hemodynamics, plasma DEET and permethrin levels, and questionnaires to assess blinding. RESULTS: Highly sensitive serologic assays readily detected DEET but not permethrin. Staff members and subjects were effectively blinded to both. The videotape-math combination was stressful by both self-report and hemodynamic measures. CONCLUSIONS: It is possible to blind subjects with respect to DEET and permethrin. Permethrin on clothing does not enter the bloodstream at appreciable levels. Combat videotapes and mental arithmetic can be stressful.

Roy MJ, Kraus PL, Seegers CA, Young SY, Kamens DR, Law WA, Cherstniakova SA, Chang DN, Cooper JA, Sato PA, Matulich W, Krantz DS, Cantilena LR, Deuster PA (2006) Pyridostigmine, diethyltoluamide, permethrin, and stress: a double-blind, randomized, placebo-controlled trial to assess safety. Mayo Clin Proc 81:1303-1310. (DoD-124)
Abstract: OBJECTIVE: To determine whether short-term human exposure to pyridostigmine bromide, diethyltoluamide, and permethrin, at rest or under stress, adversely affects short-term physical or neurocognitive performance. PARTICIPANTS AND METHODS: A multicenter, prospective, double-blind, placebo-controlled crossover trial exposing 64 volunteers to permethrin-impregnated uniforms, diethyltoluamide-containing skin cream, oral pyridostigmine, and corresponding placebos was performed. Each participant had 4 separate sessions, ensuring exposure to all treatments and placebos under both stress and rest conditions in random order. Outcomes Included physical performance (handgrip strength and duration, stair climbing, and pull-ups [males] or push-ups [females]), neurocognitive performance (computerized tests), and self-reported adverse effects. RESULTS: Permethrin was undetectable in the serum of all participants; pyridostigmine levels were higher Immediately after stress (41.6 ng/mL; 95% confidence Interval, 35.1-48.1 ng/mL) than rest (23.0 ng/mL; 95% confidence Interval, 19.2-26.9 ng/mL), whereas diethyltoluamide levels did not significantly differ by stress condition. Heart rate and systolic blood pressure increased significantly with stress compared with rest but did not vary with treatment vs placebo.

Physical and neurocognitive outcome measures and self-reported adverse effects did not significantly differ by exposure group. CONCLUSION: Combined, correct use of pyridostigmine, diethyltoluamide, and permethrin is well tolerated and without evidence of short-term physical or neurocognitive impairment.

Saeed M, Siddique N, Hung WY, Usacheva E, Liu E, Sufit RL, Heller SL, Haines JL, Pericak-Vance M, Siddique T (2006) Paraoxonase cluster polymorphisms are associated with sporadic ALS. Neurology 67:771-776.

Abstract: BACKGROUND: Paraoxonases (PONs) are involved in the detoxification of organophosphate pesticides and chemical nerve agents. Due to a reported possible twofold increased risk of ALS in Gulf War veterans and the associations of PON1 polymorphisms with the neurologic symptom complex of the Gulf War syndrome, the authors investigated the association between sporadic ALS (SALS) and PON gene cluster variants in a large North American Caucasian family-based and case-control cohort (N = 1,891). METHODS: Clinically definite and probable ALS was diagnosed according to the revised El Escorial criteria, exclusion of family history of ALS, and SOD1 mutation analysis. Single nucleotide polymorphism (SNP) genotyping was done using TaqMan assays on ABI7900HT. Data were analyzed using SPSS, Haploview, FBAT, and THESIAS. RESULTS: A haploblock of high linkage disequilibrium (LD) spanning PON2 and PON3 was associated with SALS. The SNPs rs10487132 and rs11981433 were in strong LD and associated with SALS in the trio (parents-affected child triad) model. The association of rs10487132 was replicated in 450 nuclear pedigrees comprising trios and discordant sibpairs. No association was found in case-control models, and their haplostructure was different from that of the trios with overall reduced LD. Resequencing identified an intronic variant (rs17876088) that differentiated between detrimental and protective SALS haplotypes. CONCLUSION: This study demonstrates evidence of significant association of variants in the Paraoxonase gene cluster with sporadic ALS and is compatible with the hypothesis that environmental toxicity in a susceptible host may precipitate ALS.

Salamon R, Verret C, Jutand MA, Begassat M, Laoudj F, Conso F, Brochard P (2006) Health consequences of the first Persian Gulf War on French troops. Int J Epidemiol 35:479-487. (Funded by French Ministry of Defense)

Abstract: Since 1993, many studies on the health of Persian Gulf War Veterans (PGWV) have been undertaken. These studies have concluded that there has been an increased mortality due to external causes, no excess of recognized diseases, and no effect on PGWV children. When compared with the non-deployed, PGWV have reported a higher frequency of infertility as well as different symptoms, but a specific Gulf War syndrome was not identified. In October 2000, the French government asked an independent working group to analyse the scientific literature on PGWV health. The group concluded that an exhaustive study of French PGWV was to be undertaken. The objectives of this study were to describe the exposures of PGWV in the operations theatre, to report on the symptoms and diseases that occurred in PGWV and their children during and after the military campaign, and to explore the possibility of a Gulf War syndrome. This exhaustive cross-sectional study, which included all civilians and troops who served in the Gulf from August 1990 to July 1991, began in January 2002. Data were collected by postal self-administered questionnaires. A standardized clinical evaluation was performed by 27 clinics of occupational diseases and nine military hospitals. Symptoms and diseases which appeared after the campaign are described. To date, among 20,261 PGWV, 5,666 participated in the study (28%). The most frequent symptoms described since the return from the Gulf were headaches (83%), neurological or psychological symptoms, and back pain. Apart from well-known symptoms associations (respiratory, neurocognitive, psychological and musculo-skeletal syndromes), no other cluster was highlighted by our analysis.

Sampson SM, Rome JD, Rummans TA (2006) Slow-frequency rTMS reduces fibromyalgia pain. Pain Med 7:115-118.

Abstract: OBJECTIVE: Evidence suggests that fibromyalgia (FM) is a centrally mediated pain disorder. Antidepressants, including electroconvulsive therapy, provide some symptomatic relief in FM and other pain disorders. Repetitive transcranial magnetic stimulation (rTMS) is a new antidepressant treatment, which may also be useful in treating chronic pain. DESIGN: As part of a larger study, four women with depression, FM, and borderline personality disorder received 1-Hz rTMS applied to the right dorsolateral prefrontal cortex. Subjects rated pain using an 11-point Likert scale. RESULTS: Pretreatment pain averaged 8.2 (7-9.5) and reduced to 1.5 (0-3.5) after treatment ($P < 0.009$). All had improvement in pain, and two had complete resolution of pain. Only one of the four subjects had an antidepressant response. CONCLUSIONS: These preliminary findings suggest a possible role for rTMS in treating FM.

Sarac AJ, Gur A (2006) Complementary and alternative medical therapies in fibromyalgia. Curr Pharm Des 12:47-57.
Abstract: This article describes the studies that have been performed evaluating complementary or alternative medical (CAM) therapies for efficacy and some adverse events fibromyalgia (FM). There is no permanent cure for FM; therefore, adequate symptom control should be goal of treatment. Clinicians can choose from a variety of pharmacologic and nonpharmacologic modalities. Unfortunately, controlled studies of most current treatments have failed to demonstrate sustained, clinically significant responses. CAM has gained increasing popularity, particularly among individuals with FM for which traditional medicine has generally been ineffective. Some herbal and nutritional supplements (magnesium, S- adenosylmethionine) and massage therapy have the best evidence for effectiveness with FM. Other CAM therapies such as chlorella, biofeedback, relaxation have either been evaluated in only one randomised controlled trials (RCT) with positive results, in multiple RCTs with mixed results (magnet therapies) or have positive results from studies with methodological flaws (homeopathy, botanical oils, balneotherapy, anthocyanidins and dietary modifications). Another CAM therapy such as chiropractic care has neither well-designed studies nor positive results and is not currently recommended for FM treatment. Once CAM therapies have been better evaluated for safety and long-term efficacy in randomised, placebo-controlled trials, they may prove to be beneficial in treatments for FM. It would then be important to assess studies assessing cost-benefit analyses comparing conventional therapies and CAM.

Scremin OU, Shih TM, Huynh L, Roch M, Sun W, Chialvo DR, Jenden DJ (2006) Circadian rhythms of heart rate and locomotion after treatment with low-dose acetylcholinesterase inhibitors. J Appl Toxicol 26:410-418. (DoD-113)
Abstract: This study tested the hypothesis that repeated exposure to low levels of sarin, pyridostigmine bromide (PB) or their combination, at doses equivalent to those possibly experienced by veterans of the 1991 Persian Gulf War, could lead to persistent or delayed autonomic effects and thus help to explain the cause of clinical findings in this population. Male Sprague-Dawley rats were treated for 3 weeks with: saline injection (0.5 ml kg^{-1}, s.c., 3 times weekly) with tap drinking water (control); saline injection with PB (80 mg l^{-1} in drinking water); sarin injection (62.5 µg kg^{-1}, s.c., 0.5 x LD_{50}, 3 times weekly) with tap drinking water (sarin); or sarin injection with PB in drinking water (sarin + PB). At 2, 4 or 16 weeks post-treatment, heart rate (HR) and locomotor activity (LA) were studied by radiotelemetry. Two weeks posttreatment, HR in drug-treated animals was significantly lower than in controls. A decrease in low-frequency HR power spectrum (PS) was found at 00:00 h and 08:00 h with sarin + PB and at 00:00 h with sarin, while total power was enhanced with sarin + PB at 22:00 h. Minimal effects of drug treatments on HR and HR PS were detected at 4 and 16 weeks post-treatment. No significant differences in LA between control and other groups were found. Since no consistent long-term effects were found in any of the variables studied, these experiments do not support the hypothesis that repeated administration of low doses of PB and the nerve agent sarin can induce persistent or delayed alterations in autonomic function.

Shih TM, Hulet SW, McDonough JH (2006) The effects of repeated low-dose sarin exposure. Toxicol Appl Pharmacol 215:119-134. (Funded by DoD)
Abstract: This project assessed the effects of repeated low-dose exposure of guinea pigs to the organophosphorus nerve agent sarin. Animals were injected once a day, 5 days per week (Monday-Friday), for 2 weeks with fractions (0.3x, 0.4x, 0.5x, or 0.6x) of the established LD_{50} dose of sarin (42 µg/kg, s.c.). The animals were assessed for changes in body weight, red blood cell (RBC) acetylcholinesterase (AChE) levels, neurobehavioral reactions to a functional observational battery (FOB), cortical electroencephalographic (EEG) power spectrum, and intrinsic acetylcholine (ACh) neurotransmitter (NT) regulation over the 2 weeks of sarin exposure and for up to 12 days postinjection. No guinea pig receiving 0.3, 0.4 or 0.5 x LD_{50} of sarin showed signs of cortical EEG seizures despite decreases in RBC AChE levels to as low as 10% of baseline, while seizures were evident in animals receiving 0.6 x LD_{50} of sarin as early as the second day; subsequent injections led to incapacitation and death. Animals receiving 0.5 x LD_{50} sarin showed obvious signs of cholinergic toxicity; overall, 2 of 13 animals receiving 0.5 x LD_{50} sarin died before all 10 injections were given, and there was a significant increase in the angle of gait in the animals that lived. By the 10th day of injection, the animals receiving saline were significantly easier to remove from their cages and handle and significantly less responsive to an approaching pencil and touch on the rump in comparison with the first day of testing. In contrast, the animals receiving 0.4 x LD_{50} sarin failed to show any significant reductions in their responses to an approaching pencil and a touch on the rump as compared with the first day. The 0.5 x LD_{50} sarin animals also failed to show any significant changes to the approach and touch responses and did not adjust to handling or removal from the cage from the first day of injections to the last day of handling. Thus, the guinea pigs receiving the 0.4 and 0.5 x LD_{50} doses of sarin failed to habituate to some aspects of neurobehavioral testing.

Spectral analysis of EEG data suggested that repeated sarin exposure may disrupt normal sleeping patterns (i.e., lower frequency bandwidths). While these EEG changes returned to relative normalcy 6 days after the last injection in animals receiving 0.4 x LD_{50} sarin, these changes were still observed in the animals that received 0.5 x LD(50) sarin. Ten to twelve days after the last sarin injection (in 0.4 x LD_{50} group only), neurochemical data showed that striatal choline levels were reduced in comparison to the saline group. At this time, atropine sulfate (5 mg/kg, i.p.) challenge resulted in a transient elevation in striatal ACh levels in animals exposed to repeated 0.4 x LD_{50} sarin as well as in control animals. No evidence of brain or heart pathology was found in any guinea pig that survived all 10 sarin injections.

Shih TM, Scremin OU, Roch M, Huynh L, Sun W, Jenden DJ (2006) Cerebral acetylcholine and choline contents and turnover following low-dose acetylcholinesterase inhibitors treatment in rats. Arch Toxicol 80:761-767. (DoD-113)
Abstract: Male Sprague-Dawley rats were treated for 3 weeks with (1) regular tap drinking water plus subcutaneous (s.c.) saline (0.5 ml/kg) injections three times/week, (2) pyridostigmine bromide (PB) in drinking water (80 mg/L) plus s.c. saline injections three times/week, (3) regular tap drinking water plus s.c. sarin (0.5 x LD_{50}) injections three times/week, or (4) PB in drinking water plus s.c. sarin injections three times/week. Repeated doses of sarin, in the presence or absence of PB, were devoid of acute toxicity during the three-week treatment period. Two, 4, and 16 weeks post-treatment, animals were given an intravenous pulse injection of choline labeled with 4 deuterium atoms (D4Ch) followed, after 1 min, by microwave fixation of the brain in vivo. Tissue levels of endogenous acetylcholine (D0ACh), endogenous choline (D0Ch), D4Ch, and ACh synthesized from D4Ch (D4ACh) were measured by gas-chromatography mass-spectrometry in hippocampus, infundibulum, mesencephalon, neocortex, piriform cortex, and striatum. Ch uptake from blood and ACh turnover were estimated from D4Ch and D4ACh concentrations in brain tissue, respectively. Statistically significant differences among brain regions were found for D0Ch, D4Ch, D0ACh and D4ACh at 2, 4 and 16 weeks post-treatment. However, differences in the values of these parameters between control and drug treatments were found only for D0ACh and D0Ch at 2 and 4 weeks, but not at 16 weeks post-treatment. In conclusion, the results from these experiments do not support a delayed or persistent alteration in cholinergic function after exposure to low doses of PB and/or sarin.

Siegel SD, Antoni MH, Fletcher MA, Maher K, Segota MC, Klimas N (2006) Impaired natural immunity, cognitive dysfunction, and physical symptoms in patients with chronic fatigue syndrome: preliminary evidence for a subgroup? J Psychosom Res 60:559-566.
Abstract: OBJECTIVE: The diagnostic criteria of chronic fatigue syndrome (CFS) define a heterogeneous population composed of several subgroups. Past efforts to identify subgroup markers have met with mixed success. This study was designed to examine natural killer cell activity (NKCA) as a potential subgroup marker by comparing the clinical presentations of CFS patients with and without clinically reduced NKCA. METHODS: Forty-one female CFS patients were classified into having either low or normal NKCA levels. These subgroups were then compared on objective measures of cognitive functioning and subjective assessments of fatigue, vigor, cognitive impairment, and daytime dysfunction. RESULTS: Relative to CFS patients in the normal-NKCA subgroup, low-NKCA patients reported less vigor, more daytime dysfunction, and more cognitive impairment. In addition, low-NKCA patients performed less on objective measures of cognitive functioning relative to normal-NKCA patients. CONCLUSIONS: The results are offered as preliminary evidence in support of using NKCA as an immunological subgroup marker in CFS. Findings are also discussed in terms of known associations between dysregulated immune functions, somatic symptoms, and psychological stress.

Sim M, Kelsall H (2006) Gulf War illness: a view from Australia. Philos Trans R Soc Lond B Biol Sci 361:619-626.
Abstract: Australia sent a small, mostly naval, deployment to the 1991 Gulf War. When papers and media concerns arose about unexplained Gulf War illnesses in Gulf War troops from other countries, Australia decided to undertake its own study of Australian veterans. Undertaking a later study, more than 10 years after the Gulf War, allowed us to incorporate some methodological improvements on previous research, such as the inclusion of a face-to-face health assessment where more objective health data could be collected in addition to using a postal questionnaire. Despite the different Gulf War experience for the mostly naval Australian group, there were remarkable consistencies in the patterns of multiple symptom reporting found in overseas studies, including the fact that no unique symptom clusters were identified. In general, this excess symptom reporting was not found to occur with excesses in more objective measures of physical health. These objective physical measures included a wide range of haematological, biochemical and serological markers, a physical examination, spirometry and a step test of fatigability. In contrast,

several psychological disorders, including anxiety, post-traumatic stress disorder, depression and substance abuse, were found to occur in excess in the Australian Gulf War group and were associated with Gulf War psychological stressors. These findings have helped raise awareness in Australia of psychological health problems in deployed military personnel.

Slowik A, Tomik B, Wolkow PP, Partyka D, Turaj W, Malecki MT, Pera J, Dziedzic T, Szczudlik A, Figlewicz DA (2006) Paraoxonase gene polymorphisms and sporadic ALS. Neurology 67:766-770.
Abstract: BACKGROUND: The human paraoxonase (PON) gene family consists of three members, PON1, PON2, and PON3, located adjacent to each other on chromosome 7. PON catalytic activity may be influenced by frequent amino acid variants. Chronic exposure to certain chemicals or to environmental factors causing enhanced lipid peroxidation metabolized by paraoxonases may be a risk factor for sporadic ALS (sALS). OBJECTIVE: The aim of this study was to examine the association between PON1 Q192R, PON1 L55M, and PON2 C311S functional polymorphisms and the risk of sALS in a Polish population. METHODS: The authors included 185 patients with a definite or probable diagnosis of sALS (El Escorial Criteria) and 437 healthy controls of similar age and gender. The paraoxonase polymorphisms were studied by PCR and restriction enzyme digestion. RESULTS: Using logistic regression analyses, the C allele of the C311S polymorphism was associated with sALS in dominant and additive models, whereas the R allele of the Q192R polymorphism was associated with sALS in recessive, additive, and dominant models. The authors compared the distribution of haplotypes between cases and controls. The R-C haplotype was overrepresented among cases (odds ratio 3.44, 95% CI: 1.55 to 7.62, p = 0.002). CONCLUSIONS: Frequent amino acid variants in the paraoxonase 1 and paraoxonase 2 genes are associated with sporadic ALS in a Polish population.

Smith AK, White PD, Aslakson E, Vollmer-Conna U, Rajeevan MS (2006) Polymorphisms in genes regulating the HPA axis associated with empirically delineated classes of unexplained chronic fatigue. Pharmacogenomics 7:387-394.
Abstract: Chronic fatigue syndrome (CFS) is characterized by persistent or relapsing fatigue that is not alleviated by rest, causes substantial reduction in activities and is accompanied by a variety of symptoms. Its unknown etiology may reflect that CFS is heterogeneous. Latent class analyses of symptoms and physiological systems were used to delineate subgroups within a population-based sample of fatigued and nonfatigued subjects [1]. This study examined whether genetic differences underlie the individual subgroups of the latent class solution. Polymorphisms in 11 candidate genes related to both hypothalamic-pituitary-adrenal (HPA) axis function and mood-related neurotransmitter systems were evaluated by comparing each of the five ill classes (Class 1, n = 33; Class 3, n = 22; Class 4, n = 22; Class 5, n = 17; Class 6, n = 11) of fatigued subjects with subjects defined as well (Class 2, n = 35). Of the five classes of subjects with unexplained fatigue, three classes were distinguished by gene polymorphisms involved in either HPA axis function or neurotransmitter systems, including proopiomelanocortin (POMC), nuclear receptor subfamily 3, group C, member 1 (NR3C1), monoamine oxidase A (MAOA), monoamine oxidase B (MAOB), and tryptophan hydroxylase 2 (TPH2). These data support the hypothesis that medically unexplained chronic fatigue is heterogeneous and presents preliminary evidence of the genetic mechanisms underlying some of the putative conditions.

Smith B, Smith TC, Ryan MA, Gray GC (2006) A Comparison of the postdeployment hospitalization experience of U.S. military personnel following service in the 1991 Gulf War, Southwest Asia after the Gulf War, and Bosnia. J Occup Environ Hyg 3:660-670. (DoD-096)
Abstract: Much attention has been given to the impact of deployment on the health of veterans from the 1991 Gulf War. Whereas increases in self-reported symptoms have been common, no specific exposures have been implicated. Some have suggested that stress from deployment is the chief cause for multisymptom conditions among Gulf War veterans, but comparisons with the health of other recent deployers have not been made. We sought to examine the impact of several large military deployments on hospitalization experience. Hospitalization records were examined for all active duty personnel deployed exclusively to the Gulf War, Southwest Asia after the Gulf War, or Bosnia. Cox's hazard modeling was used to assess time until first post-deployment hospitalization, separation from active duty, or December 31, 2000, whichever occurred first, while controlling for influential covariates and temporal changes. Personnel deployed to Southwest Asia after the 1991 Gulf War were at a slight increased risk for any-cause hospitalization and for 3 of the 14 major diagnostic categories when compared with veterans of the 1991 Gulf War. Personnel deployed to Bosnia were at a decreased risk for any-cause hospitalization and 12 of the 14 major diagnostic categories when compared with Gulf War veterans. These findings do not fully explain the complexity of

postdeployment health experiences. Although the risk for hospitalization may be associated with regional deployment, it is unlikely that Gulf War veterans are at greater risk of hospitalization due to a specific exposure-related disease.

Spanggord RJ, Sun M, Lim P, Ellis WY (2006) Enhancement of an analytical method for the determination of squalene in anthrax vaccine adsorbed formulations. J Pharm Biomed Anal 42:494-499. (Funded by DoD)
Abstract: Specific lots of anthrax vaccine adsorbed administered to members of the U.S. Armed Forces have been alleged to contain squalene, a chemical purported to be associated with illnesses of Gulf War veterans. A method of enhanced sensitivity for determining squalene in anthrax vaccine adsorbed using high-performance liquid chromatography with photodiode array detection has been developed, validated, and applied to 44 bottles of 38 lots of anthrax vaccine. In 43 bottles of 37 lots, no squalene was detected within a detection limit of 1ng/0.5ml dose (2 parts-per-billion). One lot, FAV008, was found to contain trace amounts of squalene at 7, 9, and 1 $\mu g l^{-1}$, levels considerably below normal human plasma levels (290 $\mu g l^{-1}$). The overall results of this investigation provide direct evidence for the absence of squalene in nearly all of anthrax vaccine preparations tested.

Spence JS, Carmack PS, Gunst RF, Schucany WR, Woodward WA, Haley RW (2006) Using a white matter reference to remove the dependency of global signal on experimental conditions in SPECT analyses. Neuroimage 32:49-53. (Funded by Perot Foundation)
Abstract: Proportional scaling models are often used in functional imaging studies to remove confounding of local signals by global effects. It is generally assumed that global effects are uncorrelated with experimental conditions. However, when the global effect is estimated by the global signal, defined as the intracerebral average, incorrect inference may result from the dependency of the global signal on preexisting conditions or experimental manipulations. In this paper, we propose a simple alternative method of estimating the global effect to be used in a proportional scaling model. Specifically, by defining the global signal with reference strictly to a white matter region within the centrum semiovale, the dependency is removed in experiments where white matter is unaffected by the disease effect or experimental treatments. The increase in the ability to detect changes in regional blood flow is demonstrated in a SPECT study of healthy and ill Gulf War veterans in whom it is suspected that brain abnormalities influence the traditional calculation of the global signal. Controlling for the global effect, ill veterans have significantly lower intracerebral averages than healthy controls ($P = 0.0038$), evidence that choice of global signal has an impact on inference. Scaling by the modified global signal proposed here results in an increase in sensitivity leading to the identification of several regions in the insula and frontal cortex where ill veterans have significantly lower SPECT emissions. Scaling by the traditional global signal results in the loss of sensitivity to detect these regional differences. Advantages of this alternative method are its computational simplicity and its ability to be easily integrated into existing analysis frameworks such as SPM.

Squibb KS, McDiarmid MA (2006) Depleted uranium exposure and health effects in Gulf War veterans. Philos Trans R Soc Lond B Biol Sci 361:639-648.
Abstract: Health effects stemming from depleted uranium (DU) exposure in a cohort of Gulf War veterans who were in or on US Army vehicles hit by friendly fire involving DU munitions are being carefully monitored through the Baltimore Veterans Affairs (VA) DU Follow-Up Program initiated in 1993. DU exposure in this cohort has been directly measured using inductively coupled plasma-mass spectrometer (ICP-MS) isotopic analysis for DU in urine specimens. Soldiers with embedded DU fragments continue to excrete elevated concentrations of U in their urine, documenting ongoing systemic exposure to U released from their fragments. Biennial surveillance visits provide a detailed health assessment that includes basic clinical measures and surveillance for early changes in kidney function, an expected target organ for U. Tests also include measurements of genotoxicity and neuroendocrine, neurocognitive and reproductive function. With the exception of the elevated urine U excretion, no clinically significant expected U-related health effects have been identified to date. Subtle changes in renal function and genotoxicity markers in veterans with urine U concentrations greater than 0.1 μg^{-1} creatinine, however, indicate the need for continued surveillance of these DU-exposed veterans.

Stevens D, Scott EA, Bowditch AP, Griffiths GD, Pearce PC (2006) Multiple vaccine and pyridostigmine interactions: effects on cognition, muscle function and health outcomes in marmosets. Pharmacol Biochem Behav 84:207-218. (Funded by UK Ministry of Defence)
Abstract: Following active service during the 1990/1991 Gulf Conflict, a number of UK and US veterans presented with a diverse range of symptoms, collectively known as Gulf Veterans Illnesses (GVI). The administration of vaccines and/or the pretreatment against possible nerve agent poisoning, pyridostigmine bromide (PB), given to

armed forces personnel during the Gulf Conflict has been implicated as a possible factor in the aetiology of these illnesses. The possibility that long-term health effects may result from the administration of these vaccines (anthrax, pertussis, plague, yellow fever, polio, typhoid, tetanus, hepatitis B, meningococcal meningitis and cholera) and/or PB, have been investigated using a non-human primate model, the common marmoset. This paper reports the results from three aspects of the study, cognitive behaviour (performance of a touchscreen mediated discrimination task), muscle function (performance of a simple strength test) and general health. There were no marked long-term changes in cognition, muscle function or health that could be attributed to vaccines and/or PB administration. Statistical differences related to treatments were only observed in two aspects of cognition and one of clinical chemistry. These changes were transient in nature and their magnitude were minor and, in consequence, was not regarded as having long-term biological significance.

Storm HH, Jorgensen HO, Kejs AM, Engholm G (2006) Depleted uranium and cancer in Danish Balkan veterans deployed 1992-2001. Eur J Cancer 42:2355-2358. (Danish Study)
Abstract: In a population based retrospective cohort study we studied cancer risk in Danish soldiers deployed to the war in the Balkans. In particular, leukaemia, earlier linked to ammunition enforced with depleted uranium (DU) in other deployed soldiers, was a concern. Military personnel, 13,552 men and 460 women, without known cancer at first deployment to the Balkans, January 1, 1992 to December 31, 2001 were followed through December 2002. We found 96cases of cancer, 84 among men (standardised incidence ratio (SIR) 0.9) and 12 among women (SIR 1.7). Only four male bone cancers (SIR 6.0), with three during the first year of follow-up, exceeded expectations. Earlier reports on increased risk of leukaemia and testis cancer among deployed military personnel to the Balkans are not corroborated by our study. Quick and open communication about potential risks, a health check, a telephone counselling line and careful monitoring, and diminished anxiety all helped contain the 'Balkan syndrome' in Denmark.

Thieme K, Flor H, Turk DC (2006) Psychological pain treatment in fibromyalgia syndrome: efficacy of operant behavioural and cognitive behavioural treatments. Arthritis Res Ther 8:R121.
Abstract: The present study focused on the evaluation of the effects of operant behavioural (OBT) and cognitive behavioural (CBT) treatments for fibromyalgia syndrome (FMS). One hundred and twenty-five patients who fulfilled the American College of Rheumatology criteria for FMS were randomly assigned to OBT (n = 43), CBT (n = 42), or an attention-placebo (AP) treatment (n = 40) that consisted of discussions of FMS-related problems. Assessments of physical functioning, pain, affective distress, and cognitive and behavioural variables were performed pre-treatment and post-treatment as well as 6 and 12 months post-treatment. Patients receiving the OBT or CBT reported a significant reduction in pain intensity post-treatment (all Fs > 3.89, all Ps < 0.01). In addition, the CBT group reported statistically significant improvements in cognitive (all Fs > 7.95, all P < 0.01) and affective variables (all Fs > 2.99, all Ps < 0.02), and the OBT group demonstrated statistically significant improvements in physical functioning and behavioural variables (all Fs > 5.99, all Ps < 0.001) compared with AP. The AP group reported no significant improvement but actually deterioration in the outcome variables. The post-treatment effects for the OBT and CBT groups were maintained at both the 6- and 12-month follow-ups. These results suggest that both OBT and CBT are effective in treating patients with FMS with some differences in the outcome measures specifically targeted by the individual treatments compared with an unstructured discussion group. The AP group showed that unstructured discussion of FMS-related problems may be detrimental.

Thomas HV, Stimpson NJ, Weightman A, Dunstan F, Lewis G (2006) Pain in veterans of the Gulf War of 1991: a systematic review. BMC Musculoskelet Disord 7:74. (Funded by UK Ministry of Defence)
Abstract: BACKGROUND: Veterans of the Persian Gulf War of 1991 have reported a range of adverse health symptoms. This systematic review aims to identify all studies that have compared the prevalence of symptoms of pain in veterans of the Gulf War to that in a non-Gulf military comparison group, and to determine whether Gulf War veterans are at increased risk of reporting pain. METHODS: Studies published between January 1990 and May 2004 were identified by searching a large number of electronic databases. Reference lists and websites were also searched and key researchers were contacted. Studies were included if they reported the prevalence of any symptom or condition that included the word "pain" in Gulf War veterans and in a comparison group of non-Gulf veterans. 2401 abstracts were independently reviewed by two authors. RESULTS: Twenty studies fulfilled the inclusion criteria. Five main sites of pain were identified (muscle, joint, chest/heart, back and abdominal pain) and separate meta-analyses were performed to summarise the results related to each site. A greater proportion of Gulf veterans reported symptoms at each site of pain when compared to a non-Gulf military group. Gulf deployment was most strongly associated with abdominal pain, with Gulf veterans being more than three times more likely to report such

pain than a comparison group (OR 3.23; 95% CI 2.31-4.51). Statistical heterogeneity between study estimates was significant, probably due to variation in measured periods of prevalence and symptom measurement methods. CONCLUSION: A higher proportion of veterans of the Persian Gulf War of 1991 reported symptoms of pain than military comparison groups. This is consistent with previously demonstrated increased reporting of more general symptoms (fatigue, multiple chemical sensitivity, post traumatic stress disorder) in these veterans compared with non-Gulf military groups. However, the primary studies were heterogeneous and varied greatly in quality.

Thomas HV, Stimpson NJ, Weightman AL, Dunstan F, Lewis G (2006) Systematic review of multi-symptom conditions in Gulf War veterans. Psychol Med 36:735-747. (Funded by UK Ministry of Defence)
Abstract: BACKGROUND: Gulf War veterans have a number of health complaints. We therefore decided to carry out a systematic review to identify and summarize the findings from studies that have assessed multi-symptom conditions in Gulf War veterans and in an unexposed comparison group. METHOD: Studies published between January 1990 and May 2004 were identified by searching a large number of electronic databases. Reference lists and websites were also searched and key researchers were contacted. Studies were included if they compared the prevalence of chronic fatigue syndrome, multiple chemical sensitivity, CDC-defined chronic multi-symptom illness, fibromyalgia, or symptoms of either fatigue or numbness and tingling in Gulf War veterans and non-Gulf veterans. A total of 2401 abstracts were independently reviewed by two authors. RESULTS: Twenty-three publications fulfilled the inclusion criteria. Gulf deployment was most strongly associated with chronic fatigue syndrome (OR 3.8, 95% CI 2.2-6.7). Gulf War veterans were also approximately three and a half times more likely than non-Gulf veterans to report multiple chemical sensitivity or chronic multi-symptom illness as defined by CDC. The methodological quality of the studies varied but the later and larger studies were of a high methodological standard with robust sampling strategies, adequate response rates and good adjustment for confounders. CONCLUSIONS: The results support the hypothesis that deployment to the Gulf War is associated with greater reporting of multi-symptom conditions.

Tissandie E, Gueguen Y, Lobaccaro JM, Grandcolas L, Voisin P, Aigueperse J, Gourmelon P, Souidi M (2007) In vivo effects of chronic contamination with depleted uranium on vitamin D(3) metabolism in rat. Biochim Biophys Acta 1770:266-272.
Abstract: The extensive use of depleted uranium (DU) in today's society results in the increase of the number of human population exposed to this radionuclide. The aim of this work was to investigate in vivo the effects of a chronic exposure to DU on vitamin D_3 metabolism, a hormone essential in mineral and bone homeostasis. The experiments were carried out in rats after a chronic contamination for 9 months by DU through drinking water at 40 mg/L (1 mg/rat/day). This dose corresponds to the double of highest concentration found naturally in Finland. In DU-exposed rats, the active vitamin D ($1,25(OH)_2D_3$) plasma level was significantly decreased. In kidney, a decreased gene expression was observed for cyp24a1, as well as for vdr and rxra, the principal regulators of CYP24A1. Similarly, mRNA levels of vitamin D target genes ecac1, cabp-d28k and ncx-1, involved in renal calcium transport were decreased in kidney. In the brain lower levels of messengers were observed for cyp27a1 as well as for lxrbeta, involved in its regulation. In conclusion, this study showed for the first time that DU affects both the vitamin D active form ($1,25(OH)_2D_3$) level and the vitamin D receptor expression, and consequently could modulate the expression of cyp24a1 and vitamin D target genes involved in calcium homeostasis.

Tissandie E, Gueguen Y, Lobaccaro JM, Paquet F, Aigueperse J, Souidi M (2006) Effects of depleted uranium after short-term exposure on vitamin D metabolism in rat. Arch Toxicol 80:473-480. (Funded by French Government: Institute for Radiological Protection and Nuclear Safety)
Abstract: Uranium is a natural radioactive heavy metal. Its toxicity has been demonstrated for different organs, including bone, kidney, liver and brain. Effects of an acute contamination by depleted uranium (DU) were investigated in vivo on vitamin D_3 biosynthetic pathway. Rats received an intragastric administration of DU (204 mg/kg) and various parameters were studied either on day 1 or day 3 after contamination. Cytochrome P450 (CYP27A1, CYP2R1, CYP27B1, CYP24A1) enzymes involved in vitamin D metabolism and two vitamin D(3)-target genes (ECaC1, CaBP-D9K) were assessed by real time RT-PCR in liver and kidneys. CYP27A1 activity was measured in liver and vitamin D and parathyroid hormone (PTH) level were measured in plasma. In acute treated-rats, vitamin D level was increased by 62% and decreased by 68% in plasma, respectively at day 1 and at day 3, which paralleled with a concomitant decrease of PTH level (90%) at day 3. In liver, cyp2r1 mRNA level was increased at day 3. Cyp27a1 activity decreased at day 1 and increased markedly at day 3. In kidney, cyp27b1 mRNA was increased at days 1 and 3 (11- and 4-fold respectively). Moreover, ecac1 and cabp-d9k mRNA levels were

increased at day 1 and decreased at day 3. This work shows for the first time that DU acute contamination modulates both activity and expression of CYP enzymes involved in vitamin D metabolism in liver and kidney, and consequently affects vitamin D target genes levels.

Vasterling JJ, Bremner JD (2006) The impact of the 1991 Gulf War on the mind and brain: findings from neuropsychological and neuroimaging research. Philos Trans R Soc Lond B Biol Sci 361:593-604.
Abstract: Many veterans of the 1991 Gulf War (GW) have complained of somatic and cognitive symptoms that may be neurological in nature. However, whether or not changes in brain function are associated with GW service continues to be debated. Studies of GW veterans using objective, performance-based neuropsychological measures have yielded inconsistent findings, with those indicating deficits among GW veterans typically revealing only relatively mild levels of neuropsychological impairment. Further, performances on objective neuropsychological tasks show little correspondence to subjective perceptions of cognitive functioning. Although preliminary magnetic resonance spectroscopy (MRS) studies demonstrate reduced N-acetylaspartate-to-creatine (NAA/Cr) ratio in select brain regions among GW veterans who report health concerns, this work requires further replication with larger, more representative samples. There is no evidence from neuroimaging studies of a non-specific effect of GW service or of changes in brain structure or function related to health status when conventional radiological methods are used. Owing to the paucity of objective exposure, baseline health data, and the now significant time elapsed since the GW, aetiological issues may never be fully resolved. Therefore, research addressing clinical management of GW veterans with neuropsychological dysfunction and neuroimaging abnormalities may prove more fruitful than exclusive focus on aetiology.

Vijayalaxmi, Kligerman AD, Prihoda TJ, Ullrich SE (2006) Micronucleus studies in the peripheral blood and bone marrow of mice treated with jet fuels, JP-8 and Jet-A. Mutat Res 608:82-87.
Abstract: The potential adverse effects of dermal and inhalation exposure of jet fuels are important for health hazard evaluation in humans. The genotoxic potential of jet fuels, JP-8 and Jet-A, was investigated in an animal model. Mice were treated dermally with either a single or multiple applications of these jet fuels. Peripheral blood and bone marrow smears were prepared to examine the incidence of micronuclei (MN) in polychromatic erythrocytes (PCEs). In all experiments, using several different exposure regimens, no statistically significant increase in the incidence of MN was observed in the bone marrow and/or peripheral blood of mice treated with JP-8 or Jet-A when compared with those of untreated control animals. The data in mice treated with a single dose of JP-8 or Jet-A did not confirm the small but statistically significant increase in micronuclei reported in our previous study.

Wan B, Fleming JT, Schultz TW, Sayler GS (2006) In vitro immune toxicity of depleted uranium: effects on murine macrophages, CD4+ T cells, and gene expression profiles. Environ Health Perspect 114:85-91.
(Funded by Waste Management Research and Education Institute & National Science Foundation)
Abstract: Depleted uranium (DU) is a by-product of the uranium enrichment process and shares chemical properties with natural and enriched uranium. To investigate the toxic effects of environmental DU exposure on the immune system, we examined the influences of DU (in the form of uranyl nitrate) on viability and immune function as well as cytokine gene expression in murine peritoneal macrophages and splenic CD4+ T cells. Macrophages and CD4+ T cells were exposed to various concentrations of DU, and cell death via apoptosis and necrosis was analyzed using annexin-V/propidium iodide assay. DU cytotoxicity in both cell types was concentration dependent, with macrophage apoptosis and necrosis occurring within 24 hr at 100 µM DU exposure, whereas CD4+ T cells underwent cell death at 500 µM DU exposure. Noncytotoxic concentrations for macrophages and CD4+ T cells were determined as 50 and 100 µM, respectively. Lymphoproliferation analysis indicated that macrophage accessory cell function was altered with 200 µM DU after exposure times as short as 2 hr. Microarray and real-time reverse-transcriptase polymerase chain reaction analyses revealed that DU alters gene expression patterns in both cell types. The most differentially expressed genes were related to signal transduction, such as c-jun, NF-k Bp65, neurotrophic factors (e.g., Mdk), chemokine and chemokine receptors (e.g., TECK/CCL25), and interleukins such as IL-10 and IL-5, indicating a possible involvement of DU in cancer development, autoimmune diseases, and T helper 2 polarization of T cells. The results are a first step in identifying molecular targets for the toxicity of DU and the elucidation of the molecular mechanisms for the immune modulation ability of DU.

Wells TS, Wang LZ, Spooner CN, Smith TC, Hiliopoulos KM, Kamens DR, Gray GC, Sato PA (2006) Self-reported reproductive outcomes among male and female 1991 Gulf War era US military veterans. Matern Child Health J 10:501-510. (DoD-001)
Abstract: BACKGROUND: Following the 1991 Gulf War, some veterans expressed concerns regarding their reproductive health. Our objective was to assess whether an association exists between deployment to the 1991 Gulf War and self-reported adverse pregnancy outcomes. METHODS: Using a modified Dillman technique with telephone follow-up, we conducted a survey via a postal questionnaire from February 1996-August 1997 to compare selected reproductive outcomes among 10,000 US veterans deployed to the 1991 Gulf War with those of 10,000 nondeployed Gulf War era veterans. RESULTS: A total of 8742 individuals responded to the survey, a response rate of 51 percent. Using multivariable analyses, results showed no differences in number of reported pregnancies between Gulf War veterans and nondeployed veterans. Among 2233 female and 2159 male participants, there were no differences in birth weight of infants born to Gulf War veterans compared with nondeployed Gulf War era veterans. In multivariable models, male and female Gulf War veterans did not significantly differ in risk for ectopic pregnancies, stillbirths, or miscarriages when compared with nondeployed veterans of the same era. CONCLUSIONS: These results do not suggest an association between service in the 1991 Gulf War and adverse reproductive outcomes for both male and female veterans during the 4 years after the war.

Whistler T, Taylor R, Craddock RC, Broderick G, Klimas N, Unger ER (2006) Gene expression correlates of unexplained fatigue. Pharmacogenomics 7:395-405.
Abstract: Quantitative trait analysis (QTA) can be used to test whether the expression of a particular gene significantly correlates with some ordinal variable. To limit the number of false discoveries in the gene list, a multivariate permutation test can also be performed. The purpose of this study is to identify peripheral blood gene expression correlates of fatigue using quantitative trait analysis on gene expression data from 20,000 genes and fatigue traits measured using the multidimensional fatigue inventory (MFI). A total of 839 genes were statistically associated with fatigue measures. These mapped to biological pathways such as oxidative phosphorylation, gluconeogenesis, lipid metabolism, and several signal transduction pathways. However, more than 50% are not functionally annotated or associated with identified pathways. There is some overlap with genes implicated in other studies using differential gene expression. However, QTA allows detection of alterations that may not reach statistical significance in class comparison analyses, but which could contribute to disease pathophysiology. This study supports the use of phenotypic measures of chronic fatigue syndrome (CFS) and QTA as important for additional studies of this complex illness. Gene expression correlates of other phenotypic measures in the CFS Computational Challenge (C3) data set could be useful. Future studies of CFS should include as many precise measures of disease phenotype as is practical.

Williams KE, Mann TM, Chamberlain S, Smith A, Wilson S, Griffiths GD, Bowditch AP, Scott EA, Pearce PC (2006) Multiple vaccine and pyridostigmine interactions: effects on EEG and sleep in the common marmoset. Pharmacol Biochem Behav 84:282-293. (Funded by UK Ministry of Defence)
Abstract: Following active service during the 1990/1991 Gulf conflict, a number of UK and US veterans presented with a diverse range of symptoms, collectively known as Gulf Veterans' Illnesses (GVI). The administration of vaccines and/or the pretreatment against possible nerve agent poisoning, pyridostigmine bromide (PB), given to Armed Forces personnel during the Gulf conflict has been implicated as a possible factor in the aetiology of these illnesses. The possibility that long-term health effects may result from the administration of these vaccines (anthrax, pertussis, plague, yellow fever, polio, typhoid, tetanus, hepatitis B, meningococcal meningitis and cholera) and/or PB, have been investigated using a non-human primate model, the common marmoset. This paper reports the results from two aspects of the study, brain electrical activity (EEG, collected during performance of a touchscreen mediated discrimination task) and sleep. There were no marked long-term changes in EEG or sleep patterns that could be attributed to vaccines and/or PB administration. The changes that were detected were predominantly time related and independent of treatment. Where statistical differences were detected between treatments, the magnitudes of the difference were relatively minor and therefore not regarded as having long term biological significance.

Woodward SH, Kaloupek DG, Streeter CC, Kimble MO, Reiss AL, Eliez S, Wald LL, Renshaw PF, Frederick BB, Lane B, Sheikh JI, Stegman WK, Kutter CJ, Stewart LP, Prestel RS, Arsenault NJ (2006) Hippocampal volume, PTSD, and alcoholism in combat veterans. Am J Psychiatry 163:674-681. (DoD-086)
Abstract: Studies imposing rigorous control over lifetime alcohol intake have usually not found smaller hippocampal volumes in persons with posttraumatic stress disorder. Because the majority of negative studies have used adolescent samples, it has been suggested that chronicity is a necessary condition for such findings. To test the hypothesis that a smaller hippocampus in PTSD is unrelated to comorbid alcoholism or to chronicity, this study estimated hippocampal volume in a relatively large group (N=99) of combat veterans in which PTSD, lifetime alcohol abuse/dependence, and Vietnam versus Gulf War service were crossed. In subjects with histories of alcoholism, unadjusted hippocampal volume was 9% smaller in persons with PTSD than in those without PTSD. In nonalcoholic subjects, the PTSD-related difference in hippocampal volume was 3%. The failure to observe a strong association between PTSD and hippocampal volume in nonalcoholic subjects was not ascribable to younger age, reduced PTSD chronicity, or lower PTSD symptom severity. The possibility that smaller hippocampal volume is limited to groups in which PTSD is compounded by comorbid alcoholism is not necessarily incompatible with results suggesting a smaller hippocampus is predispositional to PTSD. Further examination of the role of alcoholism and other comorbid conditions in studies of brain structure and function in PTSD appears warranted.

Woodward SH, Kaloupek DG, Streeter CC, Martinez C, Schaer M, Eliez S (2006) Decreased anterior cingulate volume in combat-related PTSD. Biol Psychiatry 59:582-587. (DoD-086)
Abstract: BACKGROUND: Neuroanatomical data point to functional relationships between the anterior cingulate cortex (ACC) and subcortical centers regulating fear, in particular, the amygdala. Functional brain imaging has disclosed divergent patterns of ACC activation in persons with posttraumatic stress disorder (PTSD). In addition, two preliminary structural imaging studies have found evidence of smaller ACC volume in PTSD. We explored associations between PTSD and ACC volume in a relatively large sample of adult combat veterans in which PTSD, lifetime alcohol abuse/dependence, and Vietnam versus Gulf War service were crossed. METHODS: Subjects were US military combat veterans of the Vietnam and Gulf Wars recruited from two metropolitan areas served by allied Department of Veterans Affairs PTSD treatment/research centers. Anterior cingulate cortex volume was analyzed as a function of grouping factors with and without adjustment for body size. RESULTS: Posttraumatic stress disorder was associated with smaller anterior cingulate cortex volume. This effect persisted in subjects without histories of alcoholism, did not interact with cohort effects, and was not modified by adjustment for body size. CONCLUSIONS: Anterior cingulate cortex volume is substantially smaller in association with combat-related PTSD, a finding broadly consistent with cingulate hypofunctionality in that disorder.

Yang JH, Lee CH, Monteiro-Riviere NA, Riviere JE, Tsang CL, Chou CC (2006) Toxicity of jet fuel aliphatic and aromatic hydrocarbon mixtures on human epidermal keratinocytes: evaluation based on in vitro cytotoxicity and interleukin-8 release. Arch Toxicol 80:508-523.
Abstract: Jet fuels are complex mixtures of aliphatic (ALI) and aromatic (ARO) hydrocarbons that vary significantly in individual cytotoxicity and proinflammatory activity in human epidermal keratinocytes (HEK). In order to delineate the toxicological interactions among individual hydrocarbons in a mixture and their contributions to cutaneous toxicity, nine ALI and five ARO hydrocarbons were each divided into five (high/medium/low cytotoxic and strong/weak IL-8 induction) groups and intra/inter-mixed to assess for their mixture effects on HEK mortality and IL-8 release. Addition of single hydrocarbon to JP-8 fuel was also evaluated for their changes in fuel dermatotoxicity. The results indicated that when hydrocarbons were mixed, HEK mortality and IL-8 release were not all predictable by their individual ability affecting these two parameters. The lowest HEK mortality (7%) and the highest IL-8 production were induced with mixtures including high cytotoxic and weak IL-8 inductive ARO hydrocarbons. Antagonistic reactions not consistently correlated with ALI carbon chain length and ARO structure were evident and carried different weight in the overall mixture toxicities. Single addition of benzene, toluene, xylene or ethylbenzene for up to tenfold in JP-8 did not increase HEK mortality while single addition of ALI hydrocarbons exhibited dose-related differential response in IL-8. In an all ALI environment, no single hydrocarbon is the dominating factor in the determination of HEK cytotoxicity while deletion of hexadecane resulted in a 2.5-fold increase in IL-8 production. Overall, decane, undecane and dodecane were the major hydrocarbons associated with high cytotoxicity while tetradecane, pentadecane and hexadecane were those which had the greatest buffering effect attenuating dermatotoxicity. The mixture effects must be considered when evaluating jet fuel toxicity to HEK.

Yehuda R (2006) Advances in understanding neuroendocrine alterations in PTSD and their therapeutic implications. Ann N Y Acad Sci 1071:137-166.
Abstract: The findings from investigations of the neuroendocrinology of posttraumatic stress disorder (PTSD) have highlighted alterations that have not historically been associated with pathologic processes, and have, accordingly, raised several questions about the nature of the findings and their relationship to PTSD. The most infamous of these observations--low cortisol levels--has been the subject of much discussion and scrutiny because the finding has been both counterintuitive, and not uniformly reproducible. This fact notwithstanding, novel therapeutic approaches to the treatment of PTSD are in large part predicated on the assumption that glucocorticoid levels may be lower in PTSD. This article summarizes important neuroendocrine observations in cortisol and provides strategies for understanding what has emerged over the past two decades, to be a complex and sometimes contradictory literature.

Yehuda R, Brand S, Yang RK (2006) Plasma neuropeptide Y concentrations in combat exposed veterans: relationship to trauma exposure, recovery from PTSD, and coping. Biol Psychiatry 59:660-663. (VA-076)
Abstract: BACKGROUND: There is emerging interest in examining the role of plasma neuropeptide Y (NPY) as a protective stress factor. METHODS: To further investigate this possibility, plasma NPY was measured in 11 nonexposed veterans, 11 combat-exposed veterans without posttraumatic stress disorder (PTSD), and 12 veterans with current PTSD. RESULTS: A significant group difference in plasma NPY ($F_{2,31} = 5.16$, $p = .012$) was observed, reflecting higher NPY levels in exposed veterans without PTSD than in nonexposed but comparable levels in veterans with current PTSD. Among those without current PTSD, veterans with past PTSD had higher NPY levels than those without past PTSD ($t_9 = 2.71$, $p = .024$). After controlling for all other variables, NPY levels were significantly predicted by extent of symptom improvement and lower combat exposure and significant at a trend level with positive coping. CONCLUSIONS: Plasma NPY levels may represent a biologic correlate of resilience to or recovery from the adverse effects of stress.

Yehuda R, Brand SR, Golier JA, Yang RK (2006) Clinical correlates of DHEA associated with post-traumatic stress disorder. Acta Psychiatr Scand 114:187-193. (DoD-084)
Abstract: OBJECTIVE: Increased plasma dehydroepiandrosterone (DHEA) and dehydroepiandrosterone-sulfate (DHEAS) have been demonstrated in post-traumatic stress disorder (PTSD), but the documented beneficial effects of these steroids in enhancing mood and cognition, as well as neuroprotection, suggest their presence in PTSD may be associated with defensive rather than maladaptive effects. METHOD: We, therefore, examined plasma DHEA, DHEAS, cortisol, and the DHEA/cortisol ratio in 40 male veterans with or without PTSD, and determined their relationships to PTSD symptom severity and symptom improvement. RESULTS: The PTSD group showed significantly higher plasma DHEA and non-significantly higher DHEAS levels as well as a significantly lower cortisol/DHEA ratio, controlling for age. Regression analyses demonstrated that DHEA and DHEAS levels could be predicted by symptom improvement and coping, whereas the cortisol/DHEA ratio was predicted by severity of childhood trauma and current symptom severity. CONCLUSION: That greater symptom improvement was related to DHEA levels may suggest for a role for these hormones in modulating recovery from PTSD.

Yehuda R, Golier JA, Tischler L, Harvey PD, Newmark R, Yang RK, Buchsbaum MS (2006) Hippocampal volume in aging combat veterans with and without post-traumatic stress disorder: Relation to risk and resilience factors. J Psychiatr Res. (VA-076 and National Institutes of Health)
Abstract: OBJECTIVE: To examine whether there are post-traumatic stress disorder (PTSD) related differences in hippocampal volume in middle-aged and elderly veterans and to examine the relationship of neuroendocrine activity, memory performance, and measures of risk and resilience for PTSD to hippocampal volume in this cohort. METHODS: Seventeen veterans with chronic PTSD and 16 veterans without chronic PTSD received an MRI scan followed by neuroendocrine assessment (24-h urinary cortisol excretion and the lysozyme $IC_{50\text{-}DEX}$, a measure of glucocorticoid receptor (GR) responsiveness), and cognitive testing. RESULTS: Veterans with PTSD did not differ from those without PTSD in hippocampal volume, but they did show significantly lower urinary cortisol levels, and poorer memory performance on the Wechsler Logical Memory test and Digit Span test. Smaller left hippocampal volumes were observed in veterans who developed PTSD in response to their first reported traumatic exposure, compared to veterans who had first experienced a traumatic event to which they did not develop PTSD, prior to experiencing a subsequent event that led to PTSD. In contrast, the two neuroendocrine measures were associated with risk factors related to early trauma exposure. CONCLUSION: Although hippocampal volume was not found to differ between subjects with and without PTSD, smaller hippocampal volumes in PTSD may be

associated with specific risk and resilience factors. These may be distinct from vulnerability markers associated with increased responsiveness to glucocorticoids and/or other neuroendocrine measures that have been observed in combat-related PTSD.

IV. RESEARCH FUNDING TRENDS

The following section provides a quantitative overview of the current research portfolio on GWVI and the evolution of the portfolio since 1997. Topics that are covered include research expenditures by VA, DoD, and HHS from FY 1997-2006, and the number of research projects in which the Federal Government has invested.

VA, DoD, and HHS sponsored a total of 330 distinct research projects on GWVI during the period of FY 1992 through FY 2006. 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). Nine projects have been dual-funded by VA and DoD, and each agency has given the project its own unique project number (DoD-115/VA-062; DoD-116/VA-063; DoD-116A/VA-063A; DoD-116B/VA-063B; D0D-118/VA-061; DoD-119/VA-055; DoD-125/VA-074; DoD-143/VA-078; and DoD-154/VA-088). In prior *Annual Reports*, the total number of funded projects was corrected for the number of dual funded projects. Starting with the 2005 *Annual Report*, this practice has been discontinued since VA and DoD may start or end funding of their portion of these projects independent of each other. Each dual-funded project is, therefore, treated as 2 distinct projects.

The numbers of new, ongoing and completed projects for FY 2000 - FY 2006 are shown in Figure IV-1. This data was compiled by reevaluation of previous *Annual Reports* and correcting for any projects that were listed as new when they were approved for funding but before actual funding began. The data has also been corrected for projects that began funding in previous years but were not identified until now (see Section V). As of September 30, 2006, 223 projects (68 percent of the 330 projects) were completed, and 107 projects (34 percent) were new or ongoing; the numbers of new and ongoing projects are shown in Figure IV-1.

The appropriated funds for FY 1997 through 2006, centrally obligated to each project, are shown in Appendix C and summarized in Table IV-1. Federal funding for GW research totaled $274.0 million during this period. Funds obligated for these projects prior to FY 1997 are not shown in either Table IV-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 FY 1996 are listed with no associated obligation ($0) in Appendix C. Federal funds for these earlier projects were reported in prior *Annual Reports to Congress*.

The distribution of new and ongoing projects within the five major Research Focus Areas is shown in Figure IV-2. For the six-year period from FY 2001 through 2006, research related to Brain and Nervous System Function and Environmental Toxicology consistently represents about 70% of the total number of open and ongoing projects. Over this period there has been a rise in the number of projects to study Brain and Nervous System Function (from ~28% to ~45%) with a concomitant decline in the number of Environmental Toxicology projects (from ~34% to ~21%). General Health and Symptoms research consistently represents ~25% of the new and ongoing projects.

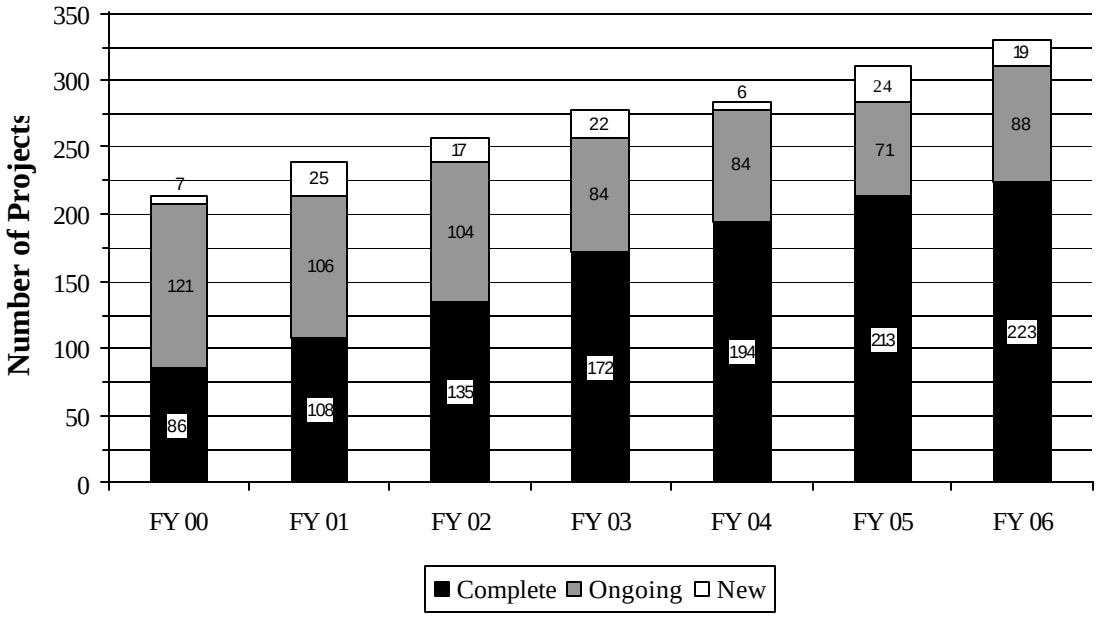

Figure IV-1. Cumulative Number of Funded Projects (FY 2000 – FY2006)

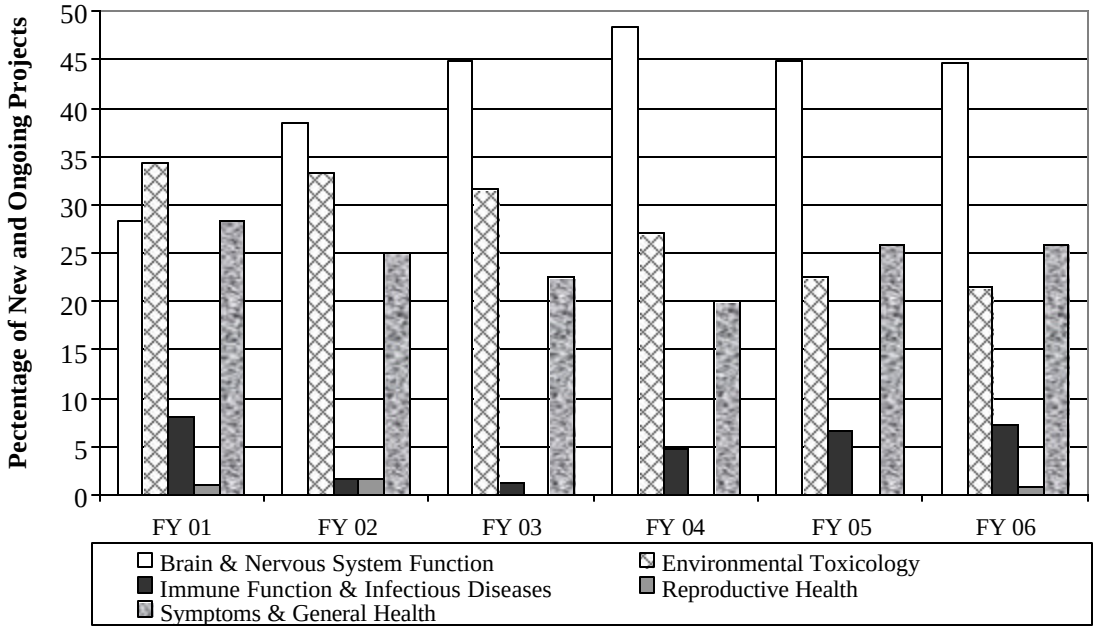

Figure IV-2. Distribution of Topic Areas for New and Ongoing Projects

Table IV-1. 10-Year (FY 1997-2006) Funding Trends for GW Research in Millions of Dollars

Department	FY '97	FY '98	FY '99	FY '00	FY '01	FY '02	FY '03	FY '04	FY '05	FY '06	Total Costs FY '97-'06
DoD	$28.9	$13.2	$22.7	$23.9	$31.6	$18.8	$15.9	$15.3	$11.6	$ 4.7	**$ 186.6**
HHS	$ 0.0	$ 1.6	$ 1.6	$ 1.6	$ 1.0	$ 0.8	$ 1.0	$ 0.5	$ 0.5	$ 0.5	**$ 9.1**
VA	$ 2.8	$ 4.7	$ 9.0	$12.0	$ 8.6	$ 4.5	$ 5.8	$ 7.7	$ 9.5	$12.9	**$ 77.5**
Total	**$ 31.7**	**$ 19.5**	**$ 33.3**	**$ 37.5**	**$ 41.2**	**$ 24.1**	**$ 22.7**	**$ 23.5**	**$ 21.6**	**$ 18.1**	**$ 273.2**

V. NEW RESEARCH PROJECTS AND INITIATIVES

A. New Initiatives

The Fiscal Year 2006 DoD GW Veterans' Illnesses Research Program (GWVIRP) was assigned to the US Army Medical Research and Materiel Command (USAMRMC) Congressionally Directed Medical Research Programs (CDMRP) with a budget of $5 million to fund research focused on chronic illnesses affecting GW veterans. The primary objective of the GWVIRP is to identify beneficial treatments for veterans affected by GWVI, either directly by evaluating specific treatments or indirectly by identifying pathophysiological mechanisms underlying these conditions that may subsequently be targeted to developing treatments. In response to the 2006 announcement of this program, proposals have been submitted and are currently under review.

VA has entered into a contractual agreement with the University of Texas Southwestern Medical Center for research related to illnesses affecting some veterans of the Gulf War. Projects under this contract are expected to begin funding in FY07 and FY08.

B. Portfolio Review

Currently funded projects in infectious diseases will be considered to be closed as of 2006. These projects and their prior funding will remain in Appendices A, B, and C to retain continuity with previous *Annual Reports to Congress*.

In recognition of the emerging issue of ALS following military service, surveillance of federally funded research to study the disease was increased for the preparation of this *Annual Report to Congress*. Ten of the 31 new projects identified for this Annual Report are focused on various aspects of ALS.

C. New Projects

This section highlights the new research projects that have been approved since last year's *Annual Report to Congress*. Projects proceeded by an asterisk (*) were approved for funding in prior fiscal years, but were not identified in previous *Annual Reports to Congress*. They are described below and incorporated into the tables in Appendices A, B and C.

Department of Defense (DoD)

Ten projects funded through the Congressionally Directed Medical Research Program (CDMRP) managed by DoD were identified as Gulf-War-related. These projects focused on Brain and Nervous System Function (4), Environmental Toxicology (4), and Immune Function and Infectious Diseases (2).

*DoD-157, "Novel Leishmania and Malaria Potassium Channels: Candidate Therapeutic Targets," will determine if inhibition of potassium channels by blocking drugs has anti-parasitic effects. If plasma membrane channels are identified as essential to parasite growth, infectivity, and/or virulence, then blocking agents could be designed as new therapeutic agents.

*DoD-158, "Preconceptional Paternal Exposure to Embedded Depleted Uranium Fragments: Transmission of Genetic Damage to Offspring," will examine whether male mice carrying embedded fragments of DU transmit genetic damage to their offspring. New information about potential health effects of embedded fragments of non-traditional metals such as DU will allow an update of existing fragment removal policies.

*DoD-159, "Neurotoxicity from Chronic Exposure to Depleted Uranium," tests the hypothesis that chronic exposure to DU impairs neuronal processes underlying cognitive function by altering how neurons in the hippocampus that use glutamate as a neurotransmitter function. These results will be of critical importance to U.S. armed forces in defining risk and establishing treatment modalities for DU exposures sustained in future battlefield situations and in affected Gulf War veterans.

*DoD-160, "Characterization of the Reproductive Toxicity of Depleted Uranium," will assess the potential of depleted uranium to produce reproductive or developmental toxicity. By performing research on the primary exposure route and using a valid and standardized protocol for assessing risk, the answer to whether depleted uranium can produce toxicity to the reproductive systems of adult male and female sailors and their offspring will be answered.

*DoD-161, "Glutamate Receptor Aptamers and ALS," aims to develop a new class of aptamer-based, anti-excitotoxic compounds (aptamers are RNA inhibitors). These inhibitors are water soluble in nature and are expected to selectively inhibit glutamate receptor-mediated excitotoxicity that may underlie neuronal damage in ALS. These experiments may lead to the development of new anti-excitotoxic drugs and diagnostic reagents.

*DoD-162, "Evaluation of the Effects of Multiple Immunizations Administered in a Stressful Environment on Immunologic Function," is a prospective clinical trial in a military recruit population to test the hypothesis that multiple, simultaneous vaccinations in a stressful environment induce an exaggerated Th2 immune response in addition to adverse Th2-associated symptoms. This study will contribute to existing research on the possible impact of multiple vaccinations administered under stressful conditions.

*DoD-163, "Neuroimmune Effects of Inhaling Low Dose Sarin," will examine the cellular and molecular bases of sarin-induced immunosuppression. The PI hypothesizes that the effects of sarin on the immune system might be affected by blockers of the adrenergic sympathetic nervous system or by inhibitors of adrenoceptors. The proposed studies will help in understanding the immunosuppressive properties of sarin, identify novel markers of its subclinical exposure, and suggest therapeutics to treat the immunotoxicity.

DoD-164, "Efficacy of Adjunct Sleep Interventions for PTSD (EASI-PTSD)," will investigate the efficacy and durability of prazosin and a behavioral sleep intervention for treating sleep disturbances associated with PTSD in veterans, reducing depression, anxiety, and improving health-related quality of life and perceived health. A successful trial may lead to new treatments for ill Gulf War veterans with sleep abnormalities.

DoD-165, "Biomarkers for Amyotrophic Lateral Sclerosis in Active Duty Military – BALSAM," will identify novel serum biomarkers that allow an early, more specific diagnosis of ALS compared to the current clinical standards. Functional studies investigating the role of these biomarkers in the onset and/or progression of the disease will provide new insight into possible factors responsible for the development and progression of the disease. In the long term, this knowledge could provide new targets for development of therapies to delay the progression or even cure this fatal disease.

DoD-166, "A Placebo-Controlled Trial of Prazosin vs. Paroxetine in Combat Stress-Induced PTSD Nightmares and Sleep Disturbance," is a randomized placebo-controlled trial to evaluate the efficacy and tolerability of, prazosin, an α-1 adrenergic antagonist, and paroxetine, a selective serotonin reuptake inhibitor, in combat-exposed returnees with nightmares and disrupted sleep in the context of PTSD. A successful trial may lead to new treatments for ill Gulf War veterans with sleep abnormalities.

Department of Health and Human Services (HHS)

One project focused on Brain and Nervous System Function was funded by HHS through the Institute for National Institute of Environmental Health Sciences. This project was approved for funding in 2004 and is indicated by an asterisk (*) as noted above. Although this project was listed in the 2005 Annual Report, financial data was unavailable; financial data for this project are now included in Appendix C.

*HHS-012, "Genetic Epidemiology of ALS in Veterans," will examine gene-environment interactions that may play a role in ALS pathogenesis using veteran controls frequency-matched to the VA ALS Registry patients by age, sex, ethnicity and branch of military service; environmental risk factor information collected from ALS patients and controls will be expanded to include military-specific exposure assessment. Genetic and environmental effects on disease progression will also be examined. This study will not only be of great relevance for the veteran population, but is also likely to improve our understanding of ALS in the general population.

Department of Veterans Affairs (VA)

VA initiated funding for 19 new projects during FY06 focused on Brain and Nervous System Function (5), Environmental Toxicology (4), Immune Function and Infectious Diseases (1), and Symptoms and General Health (9).

VA-130, "Tissue Factor and Gulf War-Associated Chronic Coagulopathies," will determine if an activated coagulation system is an underlying cause of some symptoms associated with GWVI. The results of this study will directly impact our understanding of the etiology of GWVI and provide new therapeutic targets for ill GW veterans.

VA-131, "Neuroendocrine Regulators and Proteomics in GW Veterans with CMI," will investigate whether abnormalities in proteins involved in neuroendocrine regulation are present in GW veterans with CMI, a symptom complex defined as 6 or more consecutive months of fatigue, mood and cognitive symptoms, and musculoskeletal pain. Research has demonstrated that CMI is common among GW veterans even ten years after the war.

VA-132, "Immunologic Mechanisms and Biomarkers in Gulf War Illness," will determine whether ill GW veterans have immune impairments compared to matched, healthy, sedentary controls and the degree to which the dysfunction overlaps with that in CFS. This study will also define the molecular biology of impaired immune function in GWI/CFS and determine the relationship between immune dysfunction in GWVI/CFS and disease severity.

VA-133, "Longitudinal Study of Gene Expression and Gene Products in Veterans with Gulf War Illness," will use microarray gene expression profiling and assays of immune function to differentiate people with GWI and CFS from healthy people. By measuring the products or processes regulated by the genes identified in the microarray analysis as having the strongest associations with CFS, potential biomarkers will be identified that will be useful in monitoring and defining the illness.

VA-134, "Autonomic Functions of Gulf War Veterans with Unexplained Illnesses," is a clinical pilot study to determine if neurological symptoms noted in GW veterans with a cluster of neurological symptoms are associated with abnormal testing for specific functions of autonomic nervous system (heart rate variability, responses to tilt table test, sympathetic skin response, thermal threshold, and plantar nerve conduction).

VA-135, "Motor Neuron Function of Gulf War Veterans with Excessive Fatigue," will determine if GW veterans with both unexplained neuromuscular symptoms and impaired mitochondrial function have reduced motor neuron number counts compared to control GW veterans and if GW veterans with unexplained neuromuscular symptoms are more likely to have impaired mitochondrial function than control GW veterans. Loss of motor neurons and altered mitochondrial function may be early signs of ALS.

VA-136, "Central Mechanisms Modulating Visceral Sensitivity," aims to provide new pathophysiological information about disordered brain-gut communication that may lead to the development of novel therapies for Veteran's with abnormalities of the gastrointestinal tract, including irritable bowel syndrome characterized by abdominal pain and altered bowel patterns.

VA-137, "Diarrhea-Predominant Irritable Bowel Syndrome in Persian Gulf Veterans," will determine if small bowel bacterial overgrowth (SBBO) is the cause of diarrhea-predominant symptoms in ill GW Veterans and if eradication of SBBO leads to improvement of symptoms.

VA-138, "Inspiratory Flow Dynamics During Sleep in GWS and the Effect of CPAP," will determine the prevalence of sleep fragmentation in ill GW veterans and measure the extent of inspiratory flow limitation (IFL). A group of ill GW veterans with IFL will be randomized to receive nasal continuous positive airway pressure (CPAP) at therapeutic pressure for three weeks to evaluate improvement in sleep fragmentation.

VA-139, "Sleep Neurobiology and Circuitry," will study the neuronal circuits (anatomy and neurotransmitters) responsible for the shift between sleep and wakefulness. It is important to investigate these circuits to identify appropriate targets for new therapies for specific sleep abnormalities.

VA-140, "Integrated Neuroimaging and Neuropathological Analysis of the Effects of Physical Activity on Progression and Therapy in ALS," will use magnetic resonance spectroscopy (MRS) and magnetic resonance imaging (MRI) technology to examine how exercise level affects the neurochemical changes in the nervous system of a transgenic mouse model of ALS and to correlate these changes with motor performance and pathological features of the disease.

VA-141, "Genetic Analysis of an Invertebrate Model of Amyotrophic Lateral Sclerosis," will analyze mechanisms involved in the neurodegenerative process using molecular and genetic tools. Proteins identified in invertebrate studies will then be studied in a human neuronal cell-line to determine if they might also be involved in neurotoxicity in humans. These studies may assist us to identify individuals at risk for developing sporadic ALS in GW veterans and identify new therapeutic targets to treat and/or prevent this disease.

VA-142, "VA Gulf War Biorepository Trust," will be a cooperative effort to collect high quality biological specimens linked to clinical information from consenting veterans for use in biomedical research on GWVI. Initial efforts will focus on collection of central nervous system tissue (brain and spinal cord).

VA-143, "The Role of Protein Oxidation in the Progression of ALS," will determine if an earlier accumulation of oxidative damage to specific proteins, could be diagnostic markers of the vulnerability of an organism to ALS and whether pyridostigmine and permethrin, which GW veterans were exposed to, will enhance protein oxidation and accelerate ALS in a transgenic mouse model.

VA-144, "Testing the Role of Permethrin on the Progression of ALS," will test the effect of permethrin, an insecticide used in the GW, on the progression of ALS in three mutant mouse models that develop ALS symptoms.

VA-145, "Proteomic Analysis of Cellular Response to Biological Warfare Agents," will use state of the art genomic and proteomic technology to investigate and characterize the response of human cells to PB, DEET, permethrin, and anthrax vaccination.

VA-146, "Direct Delivery of Neurotoxins to the Brain by an Intranasal Route," will test the effects of direct delivery of DEET and permethrin (alone and in combination) to the brain following inhalation through the nose. These studies, which will use much smaller doses of pesticides, are particularly important to determine if current safety levels need to be reconsidered.

VA-147, "The Diagnosis and Pathogenesis of Occult Leishmaniasis," will develop a real-time polymerase chain reaction (PCR) assay for detection and quantification of 4 different strains of Leishmania in tissues or blood and then use those assays to detect latent or active Leishmania infections in banked sera of ill GW veterans.

VA-148, "Profile of GW Veterans Who Applied for Undiagnosed Illness Compensation," is an epidemiologic database study to better understand the characteristics of veterans who have been compensated for undiagnosed illness and to determine the effect of this compensation decision on the veteran's use of VA healthcare services.

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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
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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
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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
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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
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DoD-041	Evaluation of Muscle Function in Persian Gulf Veterans
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DoD-045	Air Force Women's Health Surveillance Study
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DoD-048	Assessment of Genomic Instability via Chromosome 7 Inversion Frequency in a Gulf-War Syndrome Cohort vs Selected Control Groups
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DoD-050	Toxicokinetics of 0-Ethyl S-(2-Diisopropylaminoethyl) Methylphosphonothioate [(+)-VX] in Rats, Hairless Guinea Pigs and Marmosets - Identification of Metabolic Pathways
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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
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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
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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
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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
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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
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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
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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
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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)
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DoD-121	Evaluation of the Health Risks of Embedded Depleted Uranium Shrapnel During Pregnancy and Offspring Development
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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
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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
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DoD-138	Improving Blood Monitoring of Enzymes as Biomarkers of Risk from Anticholinergic Pesticides and Chemical Warfare Agents
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DoD-140	US Department of Defense Surveillance for Neoplasms in Infancy
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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
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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)
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DoD-157	Novel Leishmania and Malaria Potassium Channels: Candidate Therapeutic Targets
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DoD-159	Neurotoxicity from Chronic Exposure to Depleted Uranium
DoD-160	Characterization of the Reproductive Toxicity of Depleted Uranium
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DoD-162	Evaluation of the Effects of Multiple Immunizations Administered in a Stressful Environment on Immunologic Function
DoD-163	Neuroimmune Effects of Inhaling Low Dose Sarin
DoD-164	Efficacy of Adjunct Sleep Interventions for PTSD (EASI-PTSD)
DoD-165	Biomarkers for Amyotrophic Lateral Sclerosis in Active Duty Military – BALSAM
DoD-166	A Placebo-Controlled Trial of Prazosin vs. Paroxetine in Combat Stress-Induced PTSD Nightmares and Sleep Disturbance

DEPARTMENT OF HEALTH AND HUMAN SERVICES PROJECTS

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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
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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
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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
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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
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VA-006C	Neurotoxicity of Environmental Pollutants and Warfare Agents (Project III)
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VA-010	Memory and Attention in PTSD
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VA-013	Neurobehavioral Aspects of Persian Gulf Experiences: A Pilot Study
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VA-016	Protective Immunity in Experimental Visceral Leishmaniasis
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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
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VA-051	Psychobiological Assessment of Desert Storm Veterans
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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)
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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)
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VA-072	Roles of Paraoxonase, Butyrylcholinesterase and Stress in Unexplained Illnesses
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VA-074	A Randomized Clinical Trial for Cognitive-Behavioral Treatment for PTSD in Women (See DoD-125)
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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)
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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
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VA-095	The Role of Signal Regulatory Proteins in Astrocytomas
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VA-106	Interoceptive Stressor Conditioning: A Model for Gulf War Illness
VA-107	Evaluation of Stress Response Systems in Gulf War Veterans with CMI
VA-108	Telemedicine Treatment for Veterans with Gulf War Illness
VA-109	Effects of Stress on Memory: Brain Circuits, Mechanisms and Therapeutics

VA-110	Pain Among Gulf War Veterans: Secondary Analysis of CSP#458 Data
VA-111	T-Cell Responses to Multiple Immunizations and Stress
VA-112	National VA Amyotrophic Lateral Sclerosis Research Consortium
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VA-114	Strategies in Therapeutic Development of Neurodegenerative Diseases
VA-115	Autonomic System Changes Cause Intestinal Symptoms in Gulf War Veterans
VA-116	Quantitative Trait Genes Controlling Circadian and Sleep Behaviors
VA-117	Estimates of Cancer Prevalence in Gulf Veterans Using State Registries
VA-118	Post War Mortality from Neurologic Diseases in Gulf Veterans, 1991-2004
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VA-124	Early Life Determinants of Vulnerability to Pyridostigmine Bromide
VA-125	Effects of Gulf War Illness on Brain Structure, Function and Metabolism: MRI/MRS at 4 Tesla
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VA-128	MR Tracking of Stem Cells for Replacement Therapy in ALS
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VA-130	Tissue Factor and Gulf War-Associated Chronic Coagulopathies
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VA-133	Longitudinal Study of Gene Expression and Gene Products in Veterans with Gulf War Illness

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VA-135	Motor Neuron Function of Gulf War Veterans with Excessive Fatigue
VA-136	Central Mechanisms Modulating Visceral Sensitivity
VA-137	Diarrhea-Predominant Irritable Bowel Syndrome in Persian Gulf Veterans
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VA-139	Sleep Neurobiology and Circuitry
VA-140	Integrated Neuroimaging and Neuropathological Analysis of the Effects of Physical Activity on Progression and Therapy in ALS
VA-141	Genetic Analysis of an Invertebrate Model of Amyotrophic Lateral Sclerosis
VA-142	VA Gulf War Biorepository Trust
VA-143	The Role of Protein Oxidation in the Progression of ALS
VA-144	Testing the Role of Permethrin on the Progression of ALS
VA-145	Proteomic Analysis of Cellular Response to Biological Warfare Agents
VA-146	Direct Delivery of Neurotoxins to the Brain by an Intranasal Route
VA-147	The Diagnosis and Pathogenesis of Occult Leishmaniasis
VA-148	Profile of GW Veterans Who Applied for Undiagnosed Illness Compensation

Appendix B

Project List by Research Focus Areas

Brain and Nervous System Function

Clinical

Research Focus	Project Focus	Project	Project Title
	Diagnosis	DoD-165	Biomarkers for Amyotrophic Lateral Sclerosis in Active Duty Military - BALSAM
	Symptoms	VA-142	VA Gulf War Biorepository Trust
	Treatment; Symptoms;	DoD-166	A Placebo-Controlled Trial of Prazosin vs. Paroxetine in Combat Stress-Induced PTSD Nightmares and Sleep Disturbance
Environmental Toxicology	Symptoms; Exposure;	VA-064 A	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-005 B	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	Symptoms; Exposure;	DoD-057	Physiologic Effects of Stress in Gulf War 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	Diagnosis	DoD-090	SPECT Benzodiazepine Receptor and MR Imaging in PTSD
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	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	Symptoms	DoD-089	Limbic Blood Flow and Opiate Receptor PET in Posttraumatic Stress Disorder
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

Brain and Nervous System Function

Clinical

Research Focus	Project Focus	Project	Project Title
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	Symptoms; Exposure;	DoD-133	Odors, Deployment Stress, and Health: A Conditioning Analysis of Gulf War Syndrome
Symptoms and General Health	Diagnosis; Symptoms;	DoD-144	Psychological Health Screening: Methods and Metrics for Deployed Forces
Symptoms and General Health	Diagnosis	DoD-147	Development and Validation of the Automated Neuropsychological Assessment Metric (ANAM) for Deployment Health Monitoring Application
Symptoms and General Health	Diagnosis; Symptoms;	DoD-153	Gulf War Illness Research
Symptoms and General Health	Treatment; Symptoms;	DoD-164	Efficacy of Adjunct Sleep Interventions For PTSD (EASI- PTSD)
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-004 A	Evaluation of Cognitive Functioning of Persian Gulf Veterans
Symptoms and General Health	Symptoms	VA-004 B	Evaluation of Neurological Functioning in Persian Gulf Veterans
Symptoms and General Health	Diagnosis	VA-004 F	Validity of Computerized Tests
Symptoms and General Health	Symptoms	VA-005	East Orange Environmental Hazards Research Center Program
Symptoms and General Health	Symptoms	VA-006 A	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

Brain and Nervous System Function

Clinical

Research Focus	Project Focus	Project	Project Title
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	Treatment; Symptoms;	VA-060	Identification and Management of Sleep Disorders in Gulf War Veterans
Symptoms and General Health	Symptoms	VA-064	Boston Environmental Hazards Research Center
Symptoms and General Health	Diagnosis; Symptoms;	VA-064 B	Quantification and Validation of Structure-Function relationships through visuospatial test performance
Symptoms and General Health	Symptoms	VA-066	Physiological Responding in Posttraumatic Stress Disorder
Symptoms and General Health	Diagnosis; Symptoms;	VA-067	Olfactory Functioning in Gulf War Veterans
Symptoms and General Health	Symptoms	VA-072	Roles of Paraoxonase, Butyrylcholinesterase and Stress in Unexplained Illnesses
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	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
Symptoms and General Health	Symptoms	VA-085	Associative Learning in Veterans with and without Combat Experience
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	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

Brain and Nervous System Function

Clinical

Research Focus	Project Focus	Project	Project Title
Symptoms and General Health	Treatment	VA-112	National VA Amyotrophic Lateral Sclerosis Research Consortium
Symptoms and General Health	Diagnosis	VA-125	Effects of Gulf War Illness on Brain Structure, Function and Metabolism: MRI/MRS at 4 Tesla
Symptoms and General Health	Treatment; Symptoms;	VA-138	Inspiratory Flow Dynamics During Sleep in GWS and the Effect of CPAP
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
Symptoms and General Health	Diagnosis	VA-113	Novel Cause of Motor Neuron Disease
Symptoms and General Health	Treatment; Symptoms;	VA-128	MR Tracking of Stem Cells for Replacement Therapy in ALS

Brain and Nervous System Function

Epidemiology

Research Focus	Project Focus	Project	Project Title
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 Families
Symptoms and General Health	Diagnosis; Symptoms;	DoD-052	Female Gender and Other Potential Predictors of Functional Health Status Among Persian Gulf War Veterans
Symptoms and General Health	Symptoms	DoD-082	Feasibility of Developing a Registry of PTSD Affected Veteran Sib Pairs
Symptoms and General Health	Symptoms; Diagnosis;	DoD-104	Clinical Evaluation of a Proposed New Gulf War Syndrome
Symptoms and General Health	Symptoms	DoD-114	A Re-examination of Neuropsychological Functioning in Persian Gulf War Veterans

Brain and Nervous System Function

Epidemiology

Research Focus	Project Focus	Project	Project Title
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	Treatment; Prevention;	DoD-145	Early Intervention Research Program to Enhance Soldier Resilience
Symptoms and General Health	Diagnosis; Symptoms;	DoD-154	Prospective Assessment of Neurocognition in Future Gulf-deployed and Gulf-nondeployed Military Personnel: A Pilot Study (See also VA-088)
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	Symptoms	HHS-006	Defining Gulf War Illness
Symptoms and General Health	Diagnosis	HHS-012	Genetic 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-061	An Epidemiological Investigation into the Occurrence of Amyotrophic Lateral Sclerosis (ALS) Among Gulf War Veterans (See also DoD-118)
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	Diagnosis; Symptoms;	VA-088	Prospective Assessment of Neurocognition in Future Gulf-deployed and Gulf-nondeployed Military Personnel: A Pilot Study (See also DoD-154)
Symptoms and General Health	Symptoms	VA-110	Pain Among Gulf War Veterans: Secondary Analysis of CSP#458 Data

Brain and Nervous System Function

Mechanistic

Research Focus	Project Focus	Project	Project Title
	Treatment	DoD-161	Glutamate Receptor Aptamers and ALS
	Symptoms	VA-091	The Role of Dietary Choline in Neuroprotection
	Symptoms	VA-120	Arginase NO Synthase and Cell Death in Amyotrophic Lateral Sclerosis
	Symptoms	VA-139	Sleep Neurobiology and Circuitry

Brain and Nervous System Function

Mechanistic

Research Focus	Project Focus	Project	Project Title
	Treatment	VA-140	Integrated Neuroimaging and Neuropathological Analysis of the Effects of Physical Activity on Progression and Therapy in ALS
	Symptoms	VA-141	Genetic Analysis of an Invertebrate Model of Amyotrophic Lateral Sclerosis
Environmental Toxicology	Symptoms	VA-126	Structural Magnetic Resonance Imaging in Gulf War-Era Veterans
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 St ress 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 Psychiatric Disorders
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
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 Gliomas
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
Symptoms and General Health	Symptoms	VA-103	Hypothalamic and Basal Forebrain Regulation of Sleep and Arousal
Symptoms and General Health	Symptoms	VA-109	Effects of Stress on Memory: Brain Circuits, Mechanisms and Therapeutics
Symptoms and General Health	Treatment	VA-114	Strategies in Therapeutic Development of Neurodegenerative Diseases

Brain and Nervous System Function

Mechanistic

Research Focus	Project Focus	Project	Project Title
Symptoms and General Health	Symptoms	VA-116	Quantitative Trait Genes Controlling Circadian and Sleep Behaviors
Symptoms and General Health	Symptoms	VA-121	Genes, Environment, and Oxidative Stress in Neurodegenerative Disorders
Symptoms and General Health	Symptoms	VA-122	Role of Mitochondrial Oxidative Stress in ALS
Symptoms and General Health	Symptoms	VA-129	Glucocorticoid Responsivity in Gulf War Veterans

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-005 C	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; Symptoms;	DoD-064	Individual Differences in Neurobehavioral Effects of Pyridostigmine
Pyridostigmine Bromide; Brain and Nervous System Function	Exposure; Interactions; Symptoms	DoD-124	Randomized, Controlled Trial for Combination Treatment with Pyridostigmine, DEET, and Permethrin
Pyridostigmine Bromide; Brain and Nervous System Function	Exposure; Interactions; Symptoms	DoD-155	Neuropsychological Functioning in Gulf War Veterans Exposed to Pesticides and Pyridostigmine Bromide
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-064 C	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	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
Chemical Weapons	Exposure; Diagnosis;	DoD-138	Improving Blood Monitoring of Enzymes as Biomarkers of Risk from Anticholinergic Pesticides and Chemical Warfare Agents
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; Symptoms	DoD-016	Kuwait Oil Fire Health Risk Assessment
Symptoms and General Health	Diagnosis; Exposure;	DoD-100	Antibodies to Squalene

Environmental Toxicology

Epidemiology

Research Focus	Project Focus	Project	Project Title
Chemical Weapons	Exposure; Symptoms;	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)
Chemical Weapons	Exposure; Symptoms;	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)
Chemical Weapons; Symptoms and General Health	Exposure; Symptoms;	DoD-069	Five Year Follow-Up of Army Personnel Exposed to Chemical Warfare Agents

Environmental Toxicology

Epidemiology

Research Focus	Project Focus	Project	Project Title
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 Research

Environmental Toxicology

Mechanistic

Research Focus	Project Focus	Project	Project Title
	Exposure; Interactions;	DoD-103	Human Metabolism and Interactions of Deployment-related Chemicals
	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-004 E	The Aromatic Hydrocarbon Receptor (AhR) as a Biomarker of Susceptibility
	Exposure; Interactions;	VA-145	Proteomic Analysis of Cellular Response to Biological Warfare Agents
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	Exposure; Prevention;	DoD-159	Neurotoxicity from Chronic Exposure to Depleted Uranium
Brain and Nervous System Function	Exposure; Symptoms;	VA-144	Testing the Role of Permethrin on the Progression of ALS

Environmental Toxicology

Mechanistic

Research Focus	Project Focus	Project	Project Title
Brain and Nervous System Function	Exposure; Interactions;	VA-146	Direct Delivery of Neurotoxins to the Brain by an Intranasal Route
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 Diseases	Exposure; Interactions; Symptoms	DoD-037	Neurobehavioral and Immunological Toxicity of Pyridostigmine, Permethrin, and DEET in Male and Female Rats
Brain and Nervous System Function; Pyridostigmine Bromide	Exposure; Symptoms;	VA-143	The Role of Protein Oxidation in the Progression of ALS
Brain and Nervous System Function; Symptoms and General Health	Exposure; Symptoms;	DoD-007 A	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	Prevention; Exposure;	DoD-051	Transgenic Engineering of Cholinesterases: Tools for Exploring Cholinergic Responses
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; Interactions;	DoD-054	Assessment of Subchronic Neurobehavioral and Neuropathologic Effects in Rats Following Low-Level Sarin Exposure
Chemical Weapons; Brain and Nervous System Function	Exposure; Interactions; Symptoms	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; Symptoms;	DoD-056	Low-Level Sarin Neurotoxicity and Its Modulation by Pyridostigmine
Chemical Weapons; Brain and Nervous System Function	Exposure; Interactions; Symptoms	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; Symptoms;	DoD-062	Sarin and Pyridostigmine Interaction under Physical Stress: Neurotoxic Effects in Mice
Chemical Weapons; Brain and Nervous System Function	Exposure; Interactions; Symptoms	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; Symptoms	DoD-113	Interactions of Subsymptomatic Doses of Sarin with Pyridostigmine: Neurochemical, Behavioral, and Physiological Effects
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	Exposure; Symptoms;	DoD-152	Characterization of Intracellular Signaling Pathways Activated by Nerve Agents
Chemical Weapons; Brain and Nervous System Function	Exposure	VA-006 D	DNA Damage from Chemical Agents and Its Repair (Project IV)

Environmental Toxicology

Mechanistic

Research Focus	Project Focus	Project	Project Title
Immune Function and Infectious Diseases	Exposure; Symptoms;	DoD-163	Neuroimmune Effects of Inhaling Low Dose Sarin
Immune Function and Infectious Diseases;	Exposure	DoD-123	Immunotoxicity of Depleted Uranium and Heavy Metal Tungsten Alloys
Immune Function and Infectious Diseases	Exposure; Interactions;	HHS-007	Immunotoxicity of Dermal Permethrin and Cis-Urocanic Acid
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	Exposure; Interactions;	DoD-010	Pyridostigmine Synergistic Toxicity Study
Pyridostigmine Bromide	Prevention; Exposure;	DoD-033	Effects of Pyridostigmine in Flinders Line Rats Differing in Cholinergic Sensitivity
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; Symptoms;	DoD-059	Pyridostigmine-induced Neurodegeneration: Role of neuronal Apoptosis
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; Symptoms;	DoD-078	Experimental Models of Gulf War Syndrome
Pyridostigmine Bromide; Brain and Nervous System Function	Exposure; Interactions; Symptoms	DoD-079	Time Course of Stress-induced Impairment of Blood Brain Barrier
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; Symptoms	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; Symptoms	VA-006 C	Neurotoxicity of Environmental Pollutants and Warfare Agents (Project III)
Pyridostigmine Bromide; Brain and Nervous System Function	Exposure; Symptoms;	VA-049	Sensitivity to Pyridostigmine Bromide: Persistent Neural Dysfunction
Pyridostigmine Bromide; Brain and Nervous System Function	Exposure; Interactions; Symptoms	VA-080	Neurochemical and Neurobehavioral Impact of Pyridostigmine Bromide Treatment and Stress
Pyridostigmine Bromide; Brain and Nervous System Function	Exposure; Symptoms;	VA-106	Interoceptive Stressor Conditioning: A Model for Gulf War Illness

Environmental Toxicology

Mechanistic

Research Focus	Project Focus	Project	Project Title
Pyridostigmine Bromide; Brain and Nervous System Function	Exposure; Symptoms;	VA-123	Interactions Between Maternal Care, Stress and Pyridostigmine Bromide
Pyridostigmine Bromide; Brain and Nervous System Function	Exposure; Symptoms;	VA-124	Early Life Determinants of Vulnerability to Pyridostigmine Bromide
Pyridostigmine Bromide; Symptoms and General Health	Exposure; Interactions; Symptoms	VA-005 D	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 Development
Symptoms and General Health;	Exposure	DoD-007 B	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
Symptoms and General Health	Exposure; Symptoms;	DoD-160	Characterization of the Reproductive Toxicity of Depleted Uranium
Symptoms and General Health	Exposure	VA-065	San Antonio Environmental Hazards Research Center
Symptoms and General Health	Exposure	VA-065 A	Does a variant of the human SOD2 gene increase sensitivity to hazards?
Symptoms and General Health	Exposure	VA-065 B	The contribution of FEN-1 to genetic integrity subsequent to oxidative stress
Symptoms and General Health	Exposure	VA-065 C	The importance of hydrogen peroxide detoxification in cellular protection
Symptoms and General Health	Exposure	VA-065 D	Do defective Gpx1 and ALDH2 genes increase sensitivity to environmental hazards?

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-006 E	Clinical and Epidemiology Leishmania Research
	Diagnosis	VA-147	The Diagnosis and Pathogenesis of Occult Leishmaniasis

Immune Function and Infectious Diseases

Clinical

Research Focus	Project Focus	Project	Project Title
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; Symptoms	DoD-106	The Role of Th1/Th2 cytokine balance in Gulf War-related illness
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; Diagnosis;	DoD-067	Antibacterial Treatment Method Based Upon the Excretion of Dead and Decaying Spherical Bacteria
Symptoms and General Health	Exposure; Interactions;	DoD-162	Evaluation of the Effects of Multiple Immunizations Administered in a Stressful Environment on Immunologic Function
Symptoms and General Health	Symptoms; Exposure;	VA-006 B	Clinical and Neuroendocrine Aspects of Fibromyalgia (Project II)
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-008 A	Serologic Diagnosis of Viscerotropic Leishmaniasis (VTL)
	Diagnosis	DoD-008 B	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
	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
	Treatment	DoD-157	Novel Leishmania And Malaria Potassium Channels: Candidate Therapeutic Targets
	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
	Symptoms	VA-127	Interactions of the Leishmania sp. with Mammalian Cells
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	Exposure	DoD-151	Mechanisms and Consequences of Vaccine Effects on Th1/Th2 Balance in Gulf War Veterans
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; Symptoms	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
Symptoms and General Health	Symptoms	VA-111	T Cell Responses to Multiple Immunizations and Stress

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-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
	Prevention	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
	Symptoms	DoD-001G	Epidemiologic St udies 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

Reproductive Health

Mechanistic

Research Focus	Project Focus	Project	Project Title
Environmental Toxicology	Exposure; Symptoms;	DoD-158	Preconceptional Paternal Exposure to Embedded Depleted Uranium Fragments: Transmission of Genetic Damage to Offspring

Symptoms and General Health

Clinical

Research Focus	Project Focus	Project	Project Title
	Symptoms	DoD-001 A	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	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

Symptoms and General Health

Clinical

Research Focus	Project Focus	Project	Project Title
	Treatment; Symptoms;	VA-058	Implementation and Evaluation of Gulf War Veterans' Demonstration Project
	Diagnosis; Symptoms;	VA-104	Characterization of Pain Processing Mechanisms in the Irritable Bowel Syndrome
	Treatment; Symptoms;	VA-137	Diarrhea-Predominant Irritable Bowel Syndrome in Persian Gulf Veterans
Brain and Nervous System Function;	Diagnosis; Symptoms;	DoD-031	Dysregulation of the Stress Response in the Persian Gulf 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	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
Brain and Nervous System Function	Treatment; Symptoms;	VA-059	Demonstration Treatment Program for Gulf War Veterans With Unexplained Physical Symptoms
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	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	Symptoms	VA-107	Evaluation of Stress Response Systems in Gulf War Veterans with CMI

Symptoms and General Health

Clinical

Research Focus	Project Focus	Project	Project Title
Brain and Nervous System Function	Treatment; Symptoms;	VA-108	Telemedicine Treatment for Veterans with Gulf War Illness
Brain and Nervous System Function	Symptoms	VA-134	Autonomic Functions of Gulf War Veterans with Unexplained Illnesses
Brain and Nervous System Function	Symptoms	VA-135	Motor Neuron Function of Gulf War Veterans with Excessive Fatigue

Symptoms and General Health

Epidemiology

Research Focus	Project Focus	Project	Project Title
	Symptoms	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
	Symptoms	DoD-001 E	Epidemiologic Studies of Morbidity Among Gulf War Veterans: A Search for Etiologic Agents and Risk Factors; Study 5: Seabee Health Study
	Symptoms	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: 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	DoD-071	A Comparison of Post Deployment Hospitalization Between Vietnam and Gulf War Veterans
	Symptoms; Exposure;	DoD-073	Post-deployment Morbid Stress, Behavior and Health: Developing a Model for Predicting Morbidity, Mortality, and other Adverse Outcomes
	Symptoms	DoD-098	Investigation of a Baseline Medical Database to Evaluate the Health of Military Forces and Veterans
	Prevention	DoD-102	Case-Control Study of Fatal Motor Vehicle Crashes Among Gulf War and Non-Deployed Veterans

Symptoms and General Health

Epidemiology

Research Focus	Project Focus	Project	Project Title
	Prevention; Symptoms;	DoD-108	Health Status of Current National Guard Members
	Prevention	DoD-110	Predictors of Career and Family Dysfunction in Young Adults Enlisting in the United States Navy
	Symptoms	DoD-015	Comparative Mortality Among US Military Personnel Worldwide During Operations Desert Shield and Desert Storm
	Symptoms	DoD-116 B	Patterns of Pre-Persian Gulf War Illness and Health Care Seeking, Pilot Study (See also VA-63B; formerly VA/DoD-2DB)
	Prevention; Symptoms;	DoD-117	Patterns of Pre-Persian Gulf War Illness and Health Care Seeking
	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
	Prevention; Treatment;	HHS-010	Health-e Voice: Optimized Implementation of a Stepped Clinical Risk Communications Guideline
	Symptoms	HHS-011	Deployment to the Gulf War and the Subsequent Development of Cancer
	Symptoms	VA-001	Mortality Follow-up Study of Persian Gulf Veterans
	Symptoms	VA-002	National Health Survey of Persian Gulf Veterans
	Symptoms	VA-002 A	VA National Survey of Persian Gulf Veterans - Phase I
	Symptoms	VA-002 B	VA National Survey of Persian Gulf Veterans - Phase II
	Symptoms	VA-004 C	Gulf War And Vietnam Veterans Cancer Incidence Surveillance
	Symptoms	VA-046	Diarrhea in Persian Gulf Veterans: An Irritable Bowel-Like Disorder
	Symptoms	VA-063 B	Patterns of Pre-Persian Gulf War Illness and Health Care Seeking Pilot Study (See also DoD-116B; previously VA/DoD-2VB)
	Symptoms	VA-070	A Clinical Evaluation of the Health Status of Persian Gulf War Veterans in VISN 8
	Symptoms	VA-117	Estimates of Cancer Prevalence in Gulf Veterans Using State Registries

Symptoms and General Health

Epidemiology

Research Focus	Project Focus	Project	Project Title
		VA-148	Profile of GW Veterans Who Applied for Undiagnosed Illness Compensation
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-002 C	VA National Survey of Persian Gulf Veterans - Phase III
Brain and Nervous System Function	Symptoms	VA-005 A	Health and Exposure Survey of Persian Gulf Veterans
Brain and Nervous System Function	Symptoms	VA-078	Millennium Cohort Study
Brain and Nervous System Function	Symptoms	VA-118	Post War Mortality from Neurologic Diseases in Gulf Veterans, 1991-2004
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
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)
Immune Function and Infectious Diseases	Symptoms	VA-132	Immunologic Mechanisms and Biomarkers in Gulf War Illness
Immune Function and Infectious Diseases	Symptoms	VA-133	Longitudinal Study of Gene Expression and Gene Products in Veterans with Gulf War Illness
Reproductive Health	Symptoms; Prevention;	DoD-001	Naval Health Study Program
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

Symptoms and General Health

Mechanistic

Research Focus	Project Focus	Project	Project Title
	Symptoms	VA-130	Tissue Factor and Gulf War-Associated Chronic Coagulopathies
	Symptoms	VA-131	Neuroendocrine Regulators and Proteomics in GW Veterans with CMI
	Symptoms	VA-136	Central Mechanisms Modulating Visceral Sensitivity
Brain and Nervous System Function	Symptoms	VA-115	Autonomic System Changes Cause Intestinal Symptoms in Gulf War Veterans
Brain and Nervous System Function	Symptoms	VA-119	Patterns of Microarray Gene Expression in Gulf War Illness

Appendix C
Project Funding

(As of September 30, 2006)

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 1992-2005 are listed, only the financial data for FY 1996-2005 (a 10-year window) are shown in Appendix C; Totals for FY '96-'05 do not include funds obligated in FY 1992-1995. Projects that received all of their obligated funds prior to FY 1996 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.

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 nine instances (DoD-115 & VA-062, DoD-116 & VA-063, DoD-116A & VA-063A, DoD-116B & VA-063B, DoD-118 & VA-061, DoD-119 &VA-055, DoD-125 & VA-074, DoD-143 & VA-078 ,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 nine projects is broken down and reported separately by funding agency.

Department of Defense Gulf War Research Funding

PROJECT NO	PROJECT TITLE	STATUS	FY 1997	FY 1998	FY 1999	FY 2000	FY 2001	FY 2002	FY2003	FY 2004	FY 2005	FY 2006	TOTALS FY 97-06
DoD-001	Naval Health Study Program	C	$2,000,000	$2,654,000									$4,654,000
DoD-001 A	Epidemiologic Studies of Morbidity Among Gulf War Veterans: A Search for Etiologic Agents and Risk Factors; 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
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: GWV vs. NDV	C											$0

*****Totals for FY '97-'06 do not include funds obligated in FY 1992-1996

Status: C=Complete; O=Ongoing

Department of Defense Gulf War Research Funding

PROJECT NO	PROJECT TITLE	STATUS	FY 1997	FY 1998	FY 1999	FY 2000	FY 2001	FY 2002	FY2003	FY 2004	FY 2005	FY 2006	TOTALS FY 97-06
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	C											$0
DoD-002	Physiological and Neurobehavioral Effects in Rodents from Exposure to Pyridostigmine, Fuels, and DEET	C	$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	$0									$0
DoD-007 B	Carcinogenicity of Depleted Uranium Fragments	C	$0	$0	$121,400	$0							$121,400
DoD-008	Program DoD-8.	C	$695,000	$694,000	$0								$1,389,000
DoD-008 A	Serologic Diagnosis of Viscerotropic Leishmaniasis (VTL)	C											$0
DoD-008 B	Development of a Leishmania Skin Test Antigen (LSTA)	C											$0
DoD-009	Identification of the Genetic Factors Which Control Tropism in Leishmania	C	$0	$0									$0
DoD-010	Pyridostigmine Synergistic Toxicity Study	C											$0
DoD-011	Male/Female Differential Tolerances to Pyridostigmine Bromide	C	$0	$0									$0
DoD-013	Effects of Persian Gulf War Service on Military Working Dogs	C	$200,000	$120,000	$200,000	$0	$0	$0	$0				$520,000
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

*****Totals for FY '97-'06 do not include funds obligated in FY 1992-1996

Status: C=Complete; O=Ongoing

Department of Defense Gulf War Research Funding

PROJECT NO	PROJECT TITLE	STATUS	FY 1997	FY 1998	FY 1999	FY 2000	FY 2001	FY 2002	FY2003	FY 2004	FY 2005	FY 2006	TOTALS FY 97-06
DoD-016	Kuwait Oil Fire Health Risk Assessment	C	$127,000										$127,000
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	$193,000	$290,000	$295,000	$295,000	$306,000	$195,000	$225,000				$1,799,000
DoD-019	Persian Gulf Veterans Health Tracking System	C	$0	$450,000	$450,000	$0	$0	$100,000	$50,000				$1,050,000
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	$0										$0
DoD-022	Chronic Organophosphorus Exposure and Cognition	C	$0	$0	$0	$0							$0
DoD-023	Acute and Long-Term Impact of Deployment to Southwest Asia on the Physical and Mental Health of Soldiers and their Families	C	$985,000										$985,000
DoD-030	Epidemiological Studies Persian Gulf War Illnesses, PG Women's Health Linkage Study	C	$0	$0	$0	$0	$0						$0
DoD-031	Dysregulation of the Stress Response in the Persian Gulf Syndrome	C	$0	$0	$0	$0							$0
DoD-032	Neuropsychological Functioning in Persian Gulf Era Veterans	C	$0	$0	$0								$0
DoD-033	Effects of Pyridostigmine in Flinders Line Rats Differing in Cholinergic Sensitivity	C	$0	$0	$0								$0
DoD-034	Characterization of Emissions from Heaters Burning Leaded Diesel Fuel in Unvented Tents	C	$0	$0	$0								$0
DoD-035	Feasibility of Investigating Whether There is a Relationship Between Birth Defects and Service in the Gulf War.	C	$63,000	$0	$10,500	$0	$0						$73,500
DoD-036	Fatigue in Persian Gulf Syndrome-Physiologic Mechanisms	C	$0	$0	$0								$0

*****Totals for FY '97-'06 do not include funds obligated in FY 1992-1996

Status: C=Complete; O=Ongoing

Department of Defense Gulf War Research Funding

PROJECT NO	PROJECT TITLE	STATUS	FY 1997	FY 1998	FY 1999	FY 2000	FY 2001	FY 2002	FY2003	FY 2004	FY 2005	FY 2006	TOTALS FY 97-06
DoD-037	Neurobehavioral and Immunological Toxicity of Pyridostigmine, Permethrin, and DEET in Male and Female Rats	C	$0	$0	$0								$0
DoD-038	Diagnostic Antigens of Leishmania tropica	C	$0	$0									$0
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	$28,400	$155,000	$0	$124,868	$0						$308,268
DoD-040	Psychological and Neurobiological Consequences of the Gulf War Experience	C	$0	$0	$0	$0	$0						$0
DoD-041	Evaluation of Muscle Function in Persian Gulf Veterans	C	$0	$0	$0	$0							$0
DoD-042	The Symptomatic Persian Gulf Veterans Protocol: An Analysis of Risk Factors with an Immunologic and Neuropsychiatric Assessment	C	$0	$0	$0	$0	$0						$0
DoD-044	Investigation of Seminal Plasma Hypersensitivity Reactions	C	$0	$5,000	$14,200								$19,200
DoD-045	Air Force Women's Health Surveillance Study	C	$0	$456,732	$20,505	$0	$99,628	$0					$576,865
DoD-046	Exploratory Data Analysis with the CCEP Database	C	$100,000										$100,000
DoD-047	Study of Mycoplasmal Infections in Gulf War Veterans	C	$0	$0									$0
DoD-048	Assessment of Genomic Instability via Chromosome 7 Inversion Frequency in a Gulf-War Syndrome Cohort vs Selected Control Groups	C	$0	$0									$0
DoD-049	Diagnosis and Dosimetry of Exposure to Sulfur Mustard: Development of Standard Operating Procedures and Exploratory Research on Protein Adducts	C	$0	$0	$0	$0							$0
DoD-050	Toxicokinetics of 0-Ethyl S-(2-Diisopropylaminoethyl) Methylphosphonothioate [(+)-VX] in Rats, Hairless Guinea Pigs and Marmosets - Identification of Metabolic Pathways	C	$0	$0	$0								$0

*****Totals for FY '97-'06 do not include funds obligated in FY 1992-1996

Status: C=Complete; O=Ongoing

Department of Defense Gulf War Research Funding

PROJECT NO	PROJECT TITLE	STATUS	FY 1997	FY 1998	FY 1999	FY 2000	FY 2001	FY 2002	FY2003	FY 2004	FY 2005	FY 2006	TOTALS FY 97-06
DoD-051	Transgenic Engineering of Cholinesterases: Tools for Exploring Cholinergic Responses	C	$0	$0	$0	$0							$0
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	$400,000	$0	$0	$217,137	$0						$617,137
DoD-054	Assessment of Subchronic Neurobehavioral and Neuropathologic Effects in Rats Following Low-Level Sarin Exposure	C	$100,000	$0	$0	$0							$100,000
DoD-055	Low-Level Exposure to GB Vapor in Air: Diagnosis/Dosimetry, Lowest Observable Effect Levels, Performance-Incapacitation, and Possible Delayed Effects	C	$136,000	$0	$0	$0	$0						$136,000
DoD-056	Low-Level Sarin Neurotoxicity and Its Modulation by Pyridostigmine	C	$100,000	$0	$0	$0	$0						$100,000
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	$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
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

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Department of Defense Gulf War Research Funding

PROJECT NO	PROJECT TITLE	STATUS	FY 1997	FY 1998	FY 1999	FY 2000	FY 2001	FY 2002	FY2003	FY 2004	FY 2005	FY 2006	TOTALS FY 97-06
DoD-065	Multi-disciplinary Pathophysiologic Studies of Neurotoxic Gulf War Related 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	$100,000	$40,000	$403,000	$140,319	$0						$683,319
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 Exposed to Chemical Warfare Agents	O	$946,160	$0	$0	$110,000	$0	$245,910	$0	$0	$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
DoD-071	A Comparison of Post Deployment Hospitalization 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 or 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	Evaluations 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 Blood Brain Barrier	C	$100,200	$0	$0	$0							$100,200

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Department of Defense Gulf War Research Funding

PROJECT NO	PROJECT TITLE	STATUS	FY 1997	FY 1998	FY 1999	FY 2000	FY 2001	FY 2002	FY2003	FY 2004	FY 2005	FY 2006	TOTALS FY 97-06
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 to 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
DoD-083	Risk for Stress-related Substance Abuse: the Effects of Family History of Alcoholism	C	$299,700	$0	$0	$0	$0	$0					$299,700
DoD-084	Psychobiologic Alterations in Persian Gulf War Veterans with and without PTSD	C	$300,000	$0	$0	$0	$0	$0					$300,000
DoD-085	CNS 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 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 an Animal Model of Chronic Stress and Posttraumatic Stress Disorder	C	$249,700	$0	$0	$0	$0	$0					$249,700
DoD-093	Troops Exposed to Nerve Agents at Aberdeen Proving Ground: Follow-Up	C			$970,700	$0	$0						$970,700

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Department of Defense Gulf War Research Funding

PROJECT NO	PROJECT TITLE	STATUS	FY 1997	FY 1998	FY 1999	FY 2000	FY 2001	FY 2002	FY2003	FY 2004	FY 2005	FY 2006	TOTALS FY 97-06
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	C			$1,500,000	$1,500,000	$2,250,000	$1,750,000	$1,750,000	$1,750,000	$0		$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	$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	$0	$50,000	$487,333	$0	$0	$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	$2,429,999	$0	$20,833,6589
DoD-102	Case-Control Study of Fat al Motor Vehicle Crashes Among Gulf War and Non-Deployed Veterans	C			$249,908	$0	$253,793	$0	$281,950				$785,651
DoD-103	Human Metabolism and Interactions of Deployment-related Chemicals	O			$583,319	$46,315	$0	$0	$349,994	$242,424	$160,000	$326,570	$1,708,622
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	$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	$0			$886,198
DoD-108	Health Status of Current National Guard Members	C			$578,970	$0	$264,375	$174,651	$0	$0	$0		$1,017,996

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Department of Defense Gulf War Research Funding

PROJECT NO	PROJECT TITLE	STATUS	FY 1997	FY 1998	FY 1999	FY 2000	FY 2001	FY 2002	FY2003	FY 2004	FY 2005	FY 2006	TOTALS FY 97-06
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	C			$999,144	$0	$0	$0	$189,609	$0	$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	$0			$802,140
DoD-114	A Re-examination of Neuropsychological Functioning in Persian Gulf War Veterans	C			$593,712	$0	$0	$0					$593,712
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)	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/2V)	C	$250,000	$250,000	$250,000	$250,000	$250,000	$250,000	$250,000				$1,750,000
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 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 Gulf War Veterans (See also VA-61)	C				$430,824	$832,272	$0					$1,263,096

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Department of Defense Gulf War Research Funding

PROJECT NO	PROJECT TITLE	STATUS	FY 1997	FY 1998	FY 1999	FY 2000	FY 2001	FY 2002	FY2003	FY 2004	FY 2005	FY 2006	TOTALS FY 97-06
DoD-119	Antibiotic Treatment of Gulf War Veterans' Illnesses (ABT) (See also VA-55)	C			$500,000	$1,000,000	$0	$0					$1,500,000
DoD-120	Assessing the 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 During Pregnancy and Offspring Development	C	$300,000	$250,000	$25,000	$15,000	$15,000						$605,000
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 for Combination Treatment with Pyridostigmine, DEET, and Permethrin	C			$1,283,218	$0	$0	$0	$0	$0	$0		$1,283,218
DoD-125	A Randomized Clinical Trial of Cognitive-Behavioral Treatment for PTSD in Women (See VA-74)	C				$445,078	$0	$0	$0	$0	$0		$445,078
DoD-126	Blood-Brain Barrier Transport of Uranium	O				$790,884	$0	$0	$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	$89,055	$0	$1,078,945
DoD-129	Inhalation of Uranium Oxide Aerosol: CNS Deposition, Neurotoxicity, and Role in Gulf War Illness	O					$1,276,220	$0	$0	$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	$0	$0	$983,164
DoD-131	Magnetic Resonance and Spectroscopy of the Human Brain in Gulf War Illnesses	O					$5,377,526	$0	$500,000	$0	$0	$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	$0	$0	$792,198

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Department of Defense Gulf War Research Funding

PROJECT NO	PROJECT TITLE	STATUS	FY 1997	FY 1998	FY 1999	FY 2000	FY 2001	FY 2002	FY2003	FY 2004	FY 2005	FY 2006	TOTALS FY 97-06
DoD-133	Odors, Deployment Stress, and Health: A Conditioning Analysis of Gulf War Syndrome	O					$884,087	$0	$0	$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	$0	$0	$775,155
DoD-135	Biochemical Markers for Exposure to Low Doses of Organophosphorous Exposure	C				$786,408	$0	$0	$0	$0	$0		$786,408
DoD-136	A Mechanism-Based, Molecular Fingerprint Strategy for Detecting Biomarkers of Organophosphate Exposure	C					$748,858	$0	$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	$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	$0	$0	$434,795
DoD-139	Assessment of the Role of Stress-Activated Kinase in the Pathogenesis of Gulf War Illnesses	C				$892,399	$500,885	$0	$0				$1,393,284
DoD-140	US Department of Defense Surveillance for Neoplasms in Infancy	O					$764,879	$0	$0	$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	Illnesses Among Persian Gulf War Veterans: Case Validation Studies (Iowa / Great Britain)	O							$168,962	$0		$0	$168,962
DoD-143	Millennium Cohort Study	O				$3,000,000	$1,000,000	$1,250,000	$2,000,000	$1,950,000	$2,880,000	$2,893,000	$14,973,000
DoD-144	Psychological Health Screening: Methods and Metrics for Deployed Forces	O			$109,000	$295,000	$250,000	$300,000		$0	$0	$0	$954,000
DoD-145	Early Intervention Research Program to Enhance Soldier Resilience	O					$250,000	$275,000	$275,000	$0	$0	$0	$800,000

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Department of Defense Gulf War Research Funding

PROJECT NO	PROJECT TITLE	STATUS	FY 1997	FY 1998	FY 1999	FY 2000	FY 2001	FY 2002	FY2003	FY 2004	FY 2005	FY 2006	TOTALS FY 97-06
DoD-146	Assessment of Toxicology Assay Methods and Chemical Exposures Among a Cohort of US Marines Deployed in the Gulf War	C					$100,000						$100,000
DoD-147	Development and 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	$0	$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	$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 Veterans	O						$482,274	$0	$0	$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	$1,517,839	$1,500,452	$9,537,731
DoD-153	Gulf War Illness Research	O					$4,694,500	$4,950,000	$920,838	$2,003,000	$928,000	$0	$13,496,338
DoD-154	Prospective Assessment of Neurocognition in Future Gulf-deployed and Gulf-nondeployed Military Personnel: A Pilot Study (See VA-088)	O						$100,000	$566,542	$368,687	$604,372	$0	$1,639,601
DoD-155	Neuropsychological Functioning in Gulf War Veterans Exposed to Pesticides and Pyridostigmine Bromide	O							$1,021,862	$0	$0	$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	$0	$0	$1,519,951
DoD-157	Novel Leishmania And Malaria Potassium Channels: Candidate Therapeutic Targets	C					$789,805	$0	$0	$0	$0		$789,805
DoD-158	Preconceptional Paternal Exposure to Embedded Depleted Uranium Fragments: Transmission Of Genetic	O					$382,829	$0	$0	$0	$0	$0	$382,829

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Department of Defense Gulf War Research Funding

PROJECT NO	PROJECT TITLE	STATUS	FY 1997	FY 1998	FY 1999	FY 2000	FY 2001	FY 2002	FY2003	FY 2004	FY 2005	FY 2006	TOTALS FY 97-06
	Damage To Offspring												
DoD-159	Neurotoxicity from Chronic Exposure to Depleted Uranium	O					$965,931	$0	$0	$0	$0	$0	$965,931
DoD-160	Characterization of the Reproductive Toxicity of Depleted Uranium	C					$696,357	$0	$0	$0	$0		$696,357
DoD-161	Glutamate Receptor Aptamers and ALS	O							$1,152,744	$0	$0	$0	$1,152,744
DoD-162	Evaluation of the Effects of Multiple Immunizations Administered in a Stressful Environment on Immunologic Function	O							$1,041,751	$0	$0	$0	$1,041,751
DoD-163	Neuroimmune Effects of Inhaling Low Dose Sarin	O							$1,327,332	$0	$0	$0	$1,327,332
DoD-164	Efficacy of Adjunct Sleep Interventions For PTSD (EASI-PTSD)	O									$999,623	$0	$999,623
DoD-165	Biomarkers for Amyotrophic Lateral Sclerosis in Active Duty Military - BALSAM	O									$1,000,799	$0	$1,000,799
DoD-166	A Placebo-Controlled Trial of Prazosin vs. Paroxetine in Combat Stress-Induced PTSD Nightmares and Sleep Disturbance	O									$1,000,000	$0	$1,000,000
	TOTAL DOD FUNDS		**$28,880,536**	**$13,213,232**	**$22,674,338**	**$23,847,679**	**$31,587,006**	**$18,827,819**	**$15,917,953**	**$15,341,111**	**$11,609,687**	**$4,720,022**	**$186,619,383**

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Department of Health and Human Services Gulf War Research Funding

PROJECT NO	PROJECT TITLE	STATUS	FY 1997	FY 1998	FY 1999	FY 2000	FY 2001	FY 2002	FY2003	FY 2004	FY 2005	FY 2006	TOTALS FY 97-06
HHS-001	Health Assessment of Persian Gulf War Veterans from Iowa	C	$0	$0	$162,000	$0	$0						$162,000
HHS-002	Disease Cluster in a Pennsylvania Air National Guard Unit, EPI-AID 95-18	C	$0	$16,055	$0	$0							$16,055
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	$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	$0	$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	$0	$0	$1,381,177
HHS-011	Deployment to the Gulf War and the Subsequent Development of Cancer	O							$164,291	$0	$0	$0	$164,291
HHS-012	Genetic Epidemiology of ALS in Veterans	O								$466,126	$466,481	$466,000	$1,398,607
	TOTAL HHS FUNDS		**$0**	**$1,634,347**	**$1,640,378**	**$1,567,439**	**$998,870**	**$799,814**	**$964,105**	**$466,126**	**$466,481**	**$466,000**	**$9,003,560**

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Department of Veterans Affairs Gulf War Research Funding

PROJECT NO	PROJECT TITLE	STATUS	FY 1997	FY 1998	FY 1999	FY 2000	FY 2001	FY 2002	FY2003	FY 2004	FY 2005	FY 2006	TOTALS FY 97-06
VA-001	Mortality Follow-up Study of Persian Gulf Veterans	C	$440,032	$178,197	$166,848	$176,440	$171,154	$128,496	$0				$1,261,167
VA-002	National Health Survey of Persian Gulf Veterans	C						$0					$0
VA-002 A	VA National Survey of Persian Gulf Veterans - Phase I	C	$0	$18,111									$18,111
VA-002 B	VA National Survey of Persian Gulf Veterans - Phase II	C	$0	$0	$0								$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	$0	$0								$0
VA-004 TOTAL	Boston Environmental Hazards Research Center Program	C	$500,000	$500,000	$500,000	$229,500							$1,729,500
VA-004 A	Evaluat ion 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
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	$326,900							$1,826,900
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

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Department of Veterans Affairs Gulf War Research Funding

PROJECT NO	PROJECT TITLE	STATUS	FY 1997	FY 1998	FY 1999	FY 2000	FY 2001	FY 2002	FY2003	FY 2004	FY 2005	FY 2006	TOTALS FY 97-06
VA-006 TOTAL	Core Program: Portland Environmental Hazards Research Center: Environment, Veterans Health and the Gulf War Syndrome. Core Project for Clinical and Epidemiology Research	C	$499,198	$499,926	$499,098	$233,290							$1,731,512
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											$0
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											$0
VA-010	Memory and Attention in PTSD	C	$57,000	$57,600	$0								$114,600
VA-011	Neuropsychological Functioning in Veterans	C											$0
VA-012	Psychological Assessment of Operation Desert Storm Returnees	C	$0										$0
VA-013	Neurobehavioral Aspects of Persian Gulf Experiences: A Pilot Study	C											$0
VA-015	Vaccine-Mediated Immunity Against Leishmaniasis	C	$82,600	$80,000	$79,400	$41,540	$114,336	$119,600	$59,800				$577,276
VA-016	Protective Immunity in Experimental Visceral Leishmaniasis	C	$54,900										$54,900
VA-017	Immunological Evaluation of Persian Gulf Veterans	C											$0
VA-018	Chronic Gastrointestinal Illness in Persian Gulf Veterans	C											$0

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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										$0
VA-040	Musculoskeletal Symptoms in Gulf War Syndrome	C	$0	$0	$0								$0
VA-046	Diarrhea in Persian Gulf Veterans: An Irritable Bowel-Like Disorder	C	$0	$0	$0	$0							$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	$0	$0	$0	$0						$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	C			$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
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	C		$45,750	$348,225	$259,500							$653,475

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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
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	$0									$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	$0	$0								$0
VA-064	Boston Environmental Hazards Research Center	O				$112,360	$299,700	$300,000	$297,000	$337,200	$337,200	$337,200	$2,020,660
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 TOTAL	San Antonio Environmental Hazards Research Center	C				$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?	C											$0
VA-065 B	The contribution of FEN-1 to genetic integrity subsequent to oxidative stress	C											$0

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Department of Veterans Affairs Gulf War Research Funding

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VA-065 C	The importance of hydrogen peroxide detoxification in cellular protection	C											$0
VA-065 D	Do defective Gpx1 and ALDH2 genes increase sensitivity to environmental hazards?	C											$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
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-Behavio ral Treatment for PTSD in Women (See DoD-125)	C					$291,804	$896,550	$1,346,863	$1,912,448			$4,447,665
VA-075	ALS and Veterans: Are Veterans at Increased Risk?	C					$73,000	$139,600	$139,600	$78,455			$430,655
VA-076	Analysis of Hippocampal Volume in Aging Combat Veterans with PTSD	C						$145,100	$135,000	$151,740			$431,840
VA-077	HPA Axis Reactivity in Men and Women with Chronic PTSD	C						$101,400	$101,300	$113,861			$316,561
VA-078	Millennium Cohort Study	O				$0	$0	$0	$0	$0	$0	$0	$0
VA-080	Neurochemical and Neurobehavioral Impact of Pyridostigmine Bromide Treatment and Stress	O							$203,400	$119,818	$248,458	$253,277	$824,953
VA-081	Stress, Pro-Inflammatory Cytokines and Coping Behavior	C							$193,800	$186,035			$379,835

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VA-082	Pituitary Adrenal Function in People with Fatiguing Illness	O						$88,000	$135,000	$151,740	$276,112	$121,842	$772,694
VA-083	Neuropsychological Assessment of a Population-Based Sample of Persian Gulf War Veterans and Controls	C						$18,988	$50,000	$31,012			$100,000
VA-084	Neurobiology of Severe Psychological Trauma in Women	C						$135,000	$135,000	$151,740			$421,740
VA-085	Associative Learning in Veterans with and without Combat Experience	C						$60,400	$74,000	$232,459			$366,859
VA-086	A Clinical Trial of Magnetic Stimulation in Depression	C						$131,400	$131,400	$147,694			$410,494
VA-087	Improving Outcomes of Depression in Primary Care	C						$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 DoD-154)	C							$24,057	$47,011			$71,068
VA-089	National Registry of Veterans with Amyotrophic Lateral Sclerosis	O							$319,229	$625,564	$799,104	$863,951	$2,607,848
VA-090 TOTAL	Differential Gene Expression in Pathologies Associated with Neuronal Hyperexcitability: Links to Gulf War Illness	O							$250,000	$281,000	$281,000	$449,990	$1,261,990
VA-090A	Neuronal Hyperexcitability and Motor Neuron Regeneration	O											$0
VA-090B	Gene Expression and Proteomic Strategies in Severe Psychiatric Disorders	O											$0
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	C								$196,951			$196,951
VA-092	Acetylcholinesterase Activity In Gulf War Veterans	C							$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	$163,205	$127,405	$383,440

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VA-094	The Immunology of Chronic Cutaneous Leishmaniasis	O								$192,204	$157,360	$202,320	$551,884
VA-095	The Role of Signal Regulatory Proteins in Astrocytomas	O							$54,158	$231,566	$238,239	$178,679	$702,642
VA-096	Functional Imaging of Pain in Veterans with Unexplained Muscle Pain	O								$49,035	$128,698	$70,302	$248,035
VA-097	Improving a mM-CSF Tumor Vaccine for Established Intracranial Gliomas	O							$99,563	$215,093	$241,957	$246,355	$802,968
VA-098	Post-Transcriptional Gene Regulation of VEGF in Malignant Gliomas	O								$44,420	$168,600	$168,600	$381,620
VA-099	Vaccination Against Visceral Leishmaniasis with a multi-epitope vaccine	O						$65,700	$123,413	$116,896	$118,863	$117,908	$542,780
VA-100	Studies of the Blood-Brain Barrier and its Manipulation	O						$151,875	$151,875	$151,740	$151,740	$151,740	$758,970
VA-101	Biomarkers Discovery in ALS	O								$50,518	$227,130	$151,555	$429,203
VA-102	Cholinergic and Monoaminergic Influences on Sleep	O					$60,642	$92,588	$92,588	$134,160	$175,814	$134,328	$690,120
VA-103	Hypothalamic and Basal Forebrain Regulation of Sleep and Arousal	O							$210,600	$296,657	$307,253	$317,845	$1,132,355
VA-104	Characterization of Pain Processing Mechanisms in the Irritable Bowel Syndrome	O							$114,975	$168,600	$168,600	$84,300	$536,475
VA-105	Expression of the Major Surface Protease of Leishmania Chagasi	O						$76,613	$135,628	$298,175	$119,535	$92,817	$722,768
VA-106	Interoceptive Stressor Conditioning: A Model for Gulf War Illness	O									$193,440	$198,161	$391,601
VA-107	Evaluation of Stress Response Systems in Gulf War Veterans with CMI	O									$192,766	$117,412	$310,178
VA-108	Telemedicine Treatment for Veterans with Gulf War Illness	O									$185,714	$238,616	$424,330
VA-109	Effects of Stress on Memory: Brain Circuits, Mechanisms and Therapeutics	O									$158,372	$306,912	$465,284
VA-110	Pain Among Gulf War Veterans: Secondary Analysis of CSP#458 Data	O									$96,439	$48,557	$144,996

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VA-111	T Cell Responses to Multiple Immunizations and Stress	O									$112,399	$112,399	$224,798
VA-112	National VA Amyotrophic Lateral Sclerosis Research Consortium	O									$1,171,208	$734,590	$1,905,798
VA-113	Novel Cause of Motor Neuron Disease	O									$166,352	$110,152	$276,504
VA-114	Strategies in Therapeutic Development of Neurodegenerative Diseases	O									$266,950	$370,920	$637,870
VA-115	Autonomic System Changes Cause Intestinal Symptoms in Gulf War Veterans	O									$275,623	$275,623	$551,246
VA-116	Quantitative Trait Genes Controlling Circadian and Sleep Behaviors	O									$125,888	$228,734	$354,622
VA-117	Estimates of Cancer Prevalence in Gulf Veterans Using State Registries	O									$42,206	$151,740	$193,946
VA-118	Post War Mortality from Neurologic Diseases in Gulf Veterans, 1991-2004	O									$42,262	$160,535	$202,798
VA-119	Patterns of Microarray Gene Expression in Gulf War Illness	O									$192,204	$168,600	$360,804
VA-120	Arginase NO Synthase and Cell Death in Amyotrophic Lateral Sclerosis	O									$90,988	$165,116	$256,103
VA-121	Genes, Environment, and Oxidative Stress in Neurodegenerative Disorders	O									$295,938	$441,612	$737,550
VA-122	Role of Mitochondrial Oxidative Stress in ALS	O									$55,188	$271,896	$327,084
VA-123	Interactions Between Maternal Care, Stress and Pyridostigmine Bromide	O									$60,134	$48,332	$108,466
VA-124	Early Life Determinants of Vulnerability to Pyridostigmine Bromide	O									$213,110	$195,688	$408,798
VA-125	Effects of Gulf War Illness on Brain Structure, Function and Metabolism: MRI/MRS at 4 Tesla	O									$322,532	$479,892	$802,424
VA-126	Structural Magnetic Resonance Imaging in Gulf War-Era Veterans	O									$159,552	$165,565	$325,117
VA-127	Interactions of the Leishmania sp. with Mammalian Cells	O									$101,216	$166,464	$267,680

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VA-128	MR Tracking of Stem Cells for Replacement Therapy in ALS	O									$236,730	$236,730	$473,460
VA-129	Glucocorticoid Responsivity in Gulf War Veterans	O									$168,600	$167,164	$335,764
VA-130	Tissue Factor and Gulf War-Associated Chronic Coagulopathies	O										$194,826	$194,826
VA-131	Neuroendocrine Regulators and Proteomics in GW Veterans with CMI	O										$60,767	$60,767
VA-132	Immunologic Mechanisms and Biomarkers in Gulf War Illness	O										$64,630	$64,630
VA-133	Longitudinal Study of Gene Expression and Gene Products in Veterans with Gulf War Illness	O										$112,400	$112,400
VA-134	Autonomic Functions of Gulf War Veterans with Unexplained Illnesses	O										$8,880	$8,880
VA-135	Motor Neuron Function of Gulf War Veterans with Excessive Fatigue	O										$6,744	$6,744
VA-136	Central Mechanisms Modulating Visceral Sensitivity	O										$83,288	$83,288
VA-137	Diarrhea-Predominant Irritable Bowel Syndrome in Persian Gulf Veterans	O										$161,968	$161,968
VA-138	Inspiratory Flow Dynamics During Sleep in GWS and the Effect of CPAP	O										$226,773	$226,773
VA-139	Sleep Neurobiology and Circuitry	O										$33,720	$33,720
VA-140	Integrated Neuroimaging and Neuropathological Analysis of the Effects of Physical Activity on Progression and Therapy in ALS	O										$232,553	$232,553
VA-141	Genetic Analysis of an Invertebrate Model of Amyotrophic Lateral Sclerosis	O										$243,779	$243,779
VA-142	VA Gulf War Biorepository Trust	O										$991,510	$991,510
VA-143	The Role of Protein Oxidation in the Progression of ALS	O										$112,400	$112,400
VA-144	Testing the Role of Permethrin on the Progression of ALS	O										$112,400	$112,400

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VA-145	Proteomic Analysis of Cellular Response to Biological Warfare Agents	O										$129,260	$129,260
VA-146	Direct Delivery of Neurotoxins to the Brain by an Intranasal Route	O										$161,687	$161,687
VA-147	The Diagnosis and Pathogenesis of Occult Leishmaniasis	O										$98,350	$98,350
VA-148	Profile of GW Veterans Who Applied for Undiagnosed Illness Compensation	O										$24,307	$24,307
	TOTAL VA FUNDS		**$2,834,790**	**$4,722,820**	**$9,006,155**	**$12,020,519**	**$8,576,675**	**$4,512,676**	**$5,746,467**	**$7,644,560**	**$9,484,679**	**$12,942,066**	**$77,491,407**

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