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Federally Sponsored Research on Gulf War Veterans' Illnesses for 2007

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Federally Sponsored Research on Gulf War Veterans' Illnesses for 2007

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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 *2007 Annual Report to Congress*, which is the fourteenth 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) 1998 through FY 2007; and Section V highlights new research projects and initiatives.

II. RESEARCH PRIORITIES

The research priorities remain unchanged from last year. The 19 Research Topics (2 were eliminated in last year's report) 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 2007

Section III provides brief summaries of research on the health problems of GW veterans which was published in English during calendar year 2007. Research results are grouped according to the five Research Focus Areas used to organize the 19 Research Topics (see Section II): Brain and Nervous System Function, Environmental Toxicology, Immune Function, 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 2007 the Departments of Veterans Affairs (VA), Defense (DoD), and Health and Human Services (HHS) funded 345 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 $267 million for the period from FY 1998 through FY 2007. As of September 30, 2007, 272 projects (79 percent of the 345 projects) were completed, and 73 projects (21 percent) were new or ongoing.

V. NEW RESEARCH PROJECTS AND INITIATIVES

Nine projects were funded through the FY06 Gulf War Veterans' Illnesses Research Program (GWVIRP) and three were funded through the Peer Reviewed Medical Research Program (PRMRP), both managed by the Congressionally Directed Medical Research Program (CDMRP) at DoD. These projects focused on Brain and Nervous System Function (2), Environmental Toxicology (3), and Symptoms and General Health (7). Although funded from the FY06 appropriation, these projects did not actually begin until FY 2007. The two key priority areas for the FY06 GWVIRP were "Identification and evaluation of currently available treatments" and "Identification of objective indicators of pathology that distinguish ill from healthy veterans."

VA funded 2 new projects in FY 2007; one focused on Environmental Toxicology and the other on Symptoms and General Health.

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 2007*, which is the fourteenth report on research and research activities (DHWG, 2004; DHWG, 2005; DHWG, 2006a; DHWG, 2006b; DHWG, 2007; MVHCB, 2001; MVHCB, 2002; PGVCB, 1995; PGVCB, 1996b; 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 1998 through FY 2007. Section V highlights new research projects and initiatives since the last *Annual Report*.

II. RESEARCH PRIORITIES

A. Nineteen Research Topics

The Persian Gulf Veterans Coordinating Board (PGVCB) was created in 1994 to coordinate research from VA, DoD, and HHS on GWVI. In 1995, the PGVCB devised 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, 1996a), to bring the total to 21. 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*. 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 original list of 21 questions has been reduced to 19. Based on the Institute of Medicine of the National Academies (IOM) review of the scientific literature on infectious diseases (Institute of Medicine, 2006b) and the state of our current scientific knowledge, the conclusion was reached in last year's Annual Report that 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. Questions 2 and 19 have, therefore, been removed from the original list of 21 Questions and the third Research Focus Area has been refocused from Immune Function and Infectious Diseases to just Immune Function. Projects originally identified as "Gulf War research" under these two questions will continue to be listed in Appendices A and B, but no funding amounts will be shown for FY 2007 or beyond.

Similarly, PTSD-related projects that were originally included in the Federal Gulf War research portfolio will be closed as of FY2007 (i.e., no funds listed in Appendix C) if they do not directly study a population of ill Gulf War veterans or are not investigating treatments that may prove beneficial for ill Gulf War veterans.

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 Federal portfolio of Gulf War research (DHWG, 2006b). 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.

The organization of the 19 Research Topics into five major categories is described in Section B below.

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 19 Research Topics (see Section A, above).

- Brain and Nervous System Function (e.g., studies on neurological or psychological deficits and/or alterations)
  - Organic neuropsychological and neurological deficits (original Question 16)
  - Psychological symptoms and/or diagnoses (original Question 18)
- Environmental Toxicology (e.g., studies focused on specific environmental exposures such as pesticides, oil well fires, jet fuel, vaccines, medical prophylactic agents, etc.)
  - Petroleum products and combustion products (original Question 3)
  - Occupational/environmental hazards (original Question 4)
  - Organophosphorus nerve agent and/or sulfur mustard from bombing at Muhammadiyat or weapons bunker at Khamisiyah (original Question 5)
  - Chemical agents, other than at Khamisiyah (original Question 6)
  - Pyridostigmine bromide (PB) and other medical prophylaxes (e.g., vaccines and anti-malarials) (original Question 7)
  - Psychophysiological stressors (original Question 8)
  - Short term, low level exposures to pyridostigmine bromide, N,N-diethyl-m-toluamide (DEET), or permethrin, alone or in combination as a cause of short-term and/or long-term neurological effects (original Question 17)
- Immune Function (e.g., studies on alterations in immune function or host defenses)
  - Altered immune function or host defense (original Question 10)
- Reproductive Health (e.g., studies on sexual and/or reproductive dysfunction)
  - Birth defects in offspring (original Question 11)
  - Lower reproductive success (original Question 12)
  - Sexual dysfunction (original Question 13)
- Symptoms and General Health (e.g., studies on mortality, pulmonary disease, cancer, chronic multisymptom illnesses, etc.)
  - Increased prevalence or severity of symptoms and/or illnesses (original Question 1)
  - Nonspecific symptoms and symptom complexes (e.g., chronic multisymptom illnesses) (original Question 9)
  - Changes in lung function or airway reactivity (original Question 14)
  - Smaller baseline lung function or greater degree of nonspecific airway reactivity (original Question 15)
  - Development of cancers of any type (original Question 20)
  - Mortality rates (original Question 21)

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: development or testing of new therapies

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., 2002)
   e) Multiple chemical sensitivity
      (Fiedler et al., 2004; Gray et al., 2002)

2. 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, 2003; 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., 2002; 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.) Headaches
      (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)
3. 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

4. Other topics from the 19 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) Physiological responses to biological stress
   c) Sexual and/or reproductive dysfunction

III. RESEARCH RESULTS AND STATUS OF THE FIELD IN 2007

In 2007, numerous research studies provided new and detailed information on the health problems of GW veterans. A PubMed search retrieved 110 relevant articles published in English in calendar year 2007. 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 2007, followed by the PubMed abstracts. Where appropriate, 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 19 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

Studies relevant to Gulf War veterans were reviewed and are presented in this section if they provided information about the brain and nervous system, including behavioral and psychiatric disorders, neurotoxic exposures, and specific diseases such as ALS, chronic fatigue syndrome and fibromyalgia.

Publications relevant to behavioral and psychiatric disorders during 2007 included a large study reporting Gulf War deployment was associated with increased prevalence of mental disorders, psychological symptoms and a lower quality of life still evident ten years following the Gulf War (Toomey et al., 2007). Major depression and anxiety disorders were assessed in Gulf War veterans to determine their relationship to personality traits, and results suggested that depression, generalized anxiety disorder and PTSD are strongly related to personality compared to other anxiety disorders (Gamez et al., 2007). In a study of women in novel occupational roles in the UK military, Rona and colleagues found that psychological symptoms have increased over time in the non-deployed regardless of gender, and that the deployment effect in women is similar to men; psychological symptoms were positively associated with deployment in the Gulf War, but not the Iraq war (Rona et al., 2007). Levine and co-workers attempted to identify an organic basis for the neurological syndrome in Gulf War veterans but could not identify a single clinically based neurological syndrome (Levine et al., 2006). Gulf War veterans did not differ from Vietnam veterans in war-zone factors' influence on posttraumatic stress symptomatology, suggesting a similar mechanism across cohorts (Vogt and Tanner, 2007). Several recent publications from the Millenium Cohort Study described the challenges of enrolling, retaining, and following such a large cohort that is representative of the U.S. military and which promises to provide new insight into the long-term effects of military occupations on health for years to come(Riddle et al., 2007; Ryan et al., 2007). Gulf War veterans without PTSD showed significant differences in cortisol levels compared to those with PTSD, including lower 24-hour plasma ACTH and a higher cortisol:ACTH ratio (Golier et al., 2007). Barrash and colleagues judged the credibility of neuropsychological examinations in Gulf War veterans and reported that noncredible examinations were not a significant problem (Barrash et al., 2007). In a recent study Prazosin, an alpha-1 adrenergic receptor antagonist, was found to be an effective and well-tolerated treatment for trauma nightmares, sleep disturbance and global clinical status in veterans with chronic PTSD (Raskind et al., 2007).

Neurotoxic exposure studies resulted in publications on acetylcholinesterase (AChE), pyridostigmine bromide (PB), and sarin. Vaccine adjuvants were also studied in 2007. Jaga and Dharmani reviewed the literature on the interrelation between organophosphate toxicity and the epidemiology of depression and suicide (Jaga and Dharmani, 2007)**.** AChE has long been proposed as a potential factor in the illnesses affecting Gulf War veterans. Concato and co-workers reported that long-term serum activity levels were not associated with deployment to the Persian Gulf, as AChE activities was comparable for deployed and non-deployed Gulf War veterans on anxiety, mood, and symptomology (Concato et al., 2007). Mice exposed to pyridostigmine bromide (PB) and stress exhibited significant behavioral

changes including exaggerated startle response potentially related to the combined effects of PB exposure and stress; those exposed to PB or stress individually were not affected (Dubovicky et al., 2007). Gulf War veterans with presumed sarin exposure showed reduced brain white matter and increased volume in both ventricles from a magnetic imaging report (Heaton et al., 2007), suggesting subtle long-term effects from organophosphate nerve agents, e.g., Khamisiyah munitions exposure. Another result from brain imaging in the Tokyo subway exposure also showed reduced regional white matter volume in victims as well as decreased serum cholinesterase levels (Yamasue et al., 2007). Petrik and co-workers developed an animal model for examining the potential neurological impact of aluminum hydroxide, squalene, or aluminum hydroxide combined with squalene; these adjuvants may have been used in the anthrax vaccine. The results of injecting young, male rats with adjuvants at doses equivalent to those given to US military service personnel suggest a possible role for the aluminum adjuvant in some neurological features associated with GWI, and possibly an additional role for the combination of adjuvants (Petrik et al., 2007). Baireddy and co-workers concluded that while acute lethality from pyridostigmine may be increased by combined, multiple stressors, increased lethality did not appear due to enhanced cholinergic toxicity or via increased cholinesterase inhibition in either central or peripheral tissues (Baireddy et al., 2007).

Veterans determined eligible for the National Registry of Veterans with ALS were queried about their willingness to participate, and reported some small differences in refusal rates by race, VA health system use and functional status (DiMartino et al., 2007). One case study reported slowly progressive motor neuron disease following exposure to pyrethroid insecticides and suggested it was indistinguishable from ALS (Doi et al., 2006). Although a polymorphism in the paraoxonase allele PON1 Q192R had been previously suggested as a biological basis for illnesses in Gulf War veterans a new report suggest this same polymorphism is found in 60-79 year old British women, leading the investigators to conclude no causality between PON1 and illnesses affecting Gulf War veterans (Lawlor et al., 2007). In contrast, Morahan and coworkers reported genetic susceptibility to certain environmental toxicants may present risk for sporadic amyotrophic lateral sclerosis (SALS), specifically that there may be impaired detoxification conferred genetically in SALS (Morahan et al., 2007a; Morahan et al., 2007b). Sava and colleagues reported low dose administration of the mycotoxin ochratoxin-A (OTA) via minipump resulted in decreased striatal dopamine levels, important as OTA may have been stockpiled or deployed during the Gulf War (Sava et al., 2006). Smith and Lee proposed that alterations in zinc levels may initiate the development of ALS in environmental cases such as ALS in Gulf War veterans (Smith and Lee, 2007).

Functional magnetic resonance imaging (fMRI) revealed no differences in brain activity during non-fatiguing tasks such as finger tapping when comparing chronic fatigue syndrome (CFS) patients to controls, however, CFS patients showed greater activity levels in areas of the brain related to the fatiguing task relying on working memory (Cook et al., 2007a). Knoop and co-workers (2007a) examined studies investigating the effect of Cognitive Behavioral Therapy on CFS patients and reported CBT leads to a reduction in self-reported cognitive impairment, but not to improved neuropsychological test performance (Knoop et al., 2007a).

One review of fibromyalgia and neuroimaging suggested that more brain imaging research might lead to further insights for treatment possibilities (Cook et al., 2007b). Kuchinad and colleagues suggested that brain gray matter imaging showed accelerated loss in fibromyalgia patients in a pattern similar to advance age-related changes in structures including the cingulated, insular and medial frontal cortices and parahippocampal gyri (Kuchinad et al., 2007). An additional report suggested patients with primary fibromyalgia show altered brain morphology using voxel based morphometry in certain brain areas that are part of the motor system (Schmidt-Wilcke et al., 2007). Claypoole and co-workers reported finding sudden onset CFS was associated with reduced speed of information processing in a co-twin control study of 22 pairs of monozygotic twins, in which one twin met strict criteria for CFS and the co-twin was healthy (Claypoole et al., 2007).

B. Environmental Toxicology

There were scientific reports in 2007 that studied environment agents potentially toxic to GW veterans in theater. These agents can be divided into 4 groups: (1) depleted uranium (DU), which is used in armor-piercing munitions; (2) nerve agents (e.g., sarin) and anti-nerve agents (e.g., pyridostigmine bromide); (3) insecticides (e.g., permethrin, chlorpyrifos) and insecticide repellents (e.g., DEET); and (4) exposure to organic solvents (e.g., jet fuel).

Depleted Uranium (DU)

New methods for measuring uranium in human urine were developed in 2007 (Jones et al., 2007a; Oeh et al., 2007a) along with new models for the pharmacokinetics of absorbed environmental uranium (Guilmette et al., 2007). One of these new methods (Oeh et al., 2007a) was used to show that German peacekeepers exposed to DU during service in Kosovo had the same level of urinary uranium as those peacekeepers that did not serve in Kosovo and that the levels of uranium in groundwater and tap water in the area around Kosovo, where DU munitions were used, were no different than those found in other areas not exposed to DU munitions (Oeh et al., 2007b). The 2005 survey of seventy four Gulf War soldiers, who have been in this survey since 1993, with estimated exposures to DU showed no clinically significant DU-related health effects nor changes in a biomarker that measures renal proximal tubular function, a function that has been determined to be sensitive to DU exposure in both humans and other vertebrates (McDiarmid et al., 2007). Guilmette and Parkhurst described some of the difficulties in dose assessment modeling of the very complex DU aerosols created when Abrams tanks and Bradley fighting vehicles are struck with large-caliber DU penetrators. The approaches used to solve these problems along with example results were presented (Guilmette and Parkhurst, 2007).

The effects of DU in various animal models were also reported on. Rats implanted with increasing amounts of DU showed a dose-dependent increase in urinary uranium although there was no dose-dependent change in uranium tissue level. There were no measured differences in serum chemistry, monocyte ratios, mean platelet volume, gross necropsy, histological analysis, general health or behavior (Arfsten et al., 2007). Rats given intramuscular injections of DU, with and without stress, had similar brain uranium levels with no evidence of renal toxicity (Barber et al., 2007). Another study of intramuscular injection of DU in rats, with and without stress, showed a dose-dependent short-term renal effect that was not altered by stress (Zimmerman et al., 2007). In studies of rats given uranium orally changes in markers of oxidative stress in various brain regions were observed (Linares et al., 2007), as well as a time-dependent change in markers for intestinal inflammation, including an increase in intestinal immune cells (Dublineau et al., 2007). Regardless of the route of uranium exposure (i.e., oral, injection or inhalation), rats showed low tissue levels of uranium. The route of exposure did, however, influence the relative amount of uranium deposited in specific tissues (Houpert et al., 2007). Rats were also shown to absorb uranium through abraded skin quicker than intact skin (Petitot et al., 2007). Finally, Zebrafish showed signs of oxidative stress when exposed to dissolve uranium (Barillet et al., 2007).

The effects of DU and uranium on isolated cells and cellular compartments were also reported in 2007. A study using isolated human bronchial fibroblasts showed a dose-dependent toxicity to uranium as measured by cell death and DNA damage (Wise et al., 2007). Isolated rat kidney cells showed a dose-dependent sensitivity to uranium as reflected in measures of DNA damage and apoptosis (Thiebault et al., 2007). Exposure of isolated cortical neurons and nematodes to uranium elicited no detectable neurotoxic responses (Jiang et al., 2007). Viette and colleagues demonstrated that, GABA release from isolated synaptosomes was less sensitive to inhibition in the presence of uranium (Vietti and Lasley, 2007).

Nerve Agents

A study in 2007 showed that the only definitive effect of sarin exposure resulting from the 1995 terrorist attack in Japan was an increase in post-traumatic stress syndrome (Hoffman et al., 2007). Pyridostigmine bromide tablets were the only continuous exposure significantly associated with ill Gulf War veterans, with the odds of having symptoms increased by 1.3% for every tablet taken (Lucas et al., 2007).

The effects of sarin on animal models were also studied. Exposure of African Green monkeys to sarin for 10 minutes showed no changes measured parameters of toxicity other than constricted pupils of the eyes (Genovese et al., 2007a). Intramuscular injections of sarin into African Green monkeys and Rhesus monkeys did not affect any measured behavioral performance test although it did inhibit the RBC acetylcholinesterase activity (Genovese et al., 2007b). Three days after guinea pigs were injected with high-doses of sarin there was no changes in various measurements in the parietal cortex although there were changes in the DNA of leukocytes that suggested DNA damage. After three days, all measured parameters returned to normal (Dave et al., 2007). Pharmacokinetic studies of sarin were also performed in guinea pigs, including the effects on the acetylcholinesterase and butyrylcholinesterase activities in RBC (Whalley et al., 2007). Rats exposed to sarin initially had an elevation in the antibody-forming cell response test and in T-cell mitogenesis although these returned to normal values within 4 weeks. Additionally, corticosterone and adrenocorticotropic hormone were decreased and stayed decreased at 4 weeks post-exposure (Pena-Philippides et al., 2007). A study in mice showed that sarin exposure and stress resulted in short-term but not long-term changes in

measured behavior and in certain endocrine values (Mach et al., 2007). Pyridostigmine, which is used to counteract the effects of organophosphate nerve agents, was shown in rats to become more lethal if the animals were stressed before given pyridostigmine although this increased lethality does not appear to result from enhanced cholinergic activity or enhanced cholinesterase activity. The known sensitivity difference of humans to effects of organophosphates was show to possibly result from genetic difference in the gene that expresses paraoxonase, the enzyme that catabolizes organophosphates (Sirivarasai et al., 2007).

Insecticides and Pesticides

A long-term prospective study of agricultural workers in the US exposed to chlorpyrifos, one of the mostly widely-used insecticides in the US, suggested that there could be a link between exposure and depression or other neurobehavioral changes (Lee et al., 2007). Studies conducted in rats showed that subcutaneous injections of chlorpyrifos, with and without stress, did not affect changes in serum corticosterone nor did stress effect the chlorpyrifos-induced inhibition of brain acetylcholinesterase activity (Hancock et al., 2007). Rats injected with chlorpyrifos showed an effect in the brain on neurotrophin receptors and cholinergic proteins (Terry, Jr. et al., 2007). Permethrin has no effect on current amplitude in cultured isolated rat brain neurons (Meyer and Shafer, 2006). In another study the ability of chlorpyrifos to affect the catabolism of other xenobiotics, including DEET by the human cytochrome P450 system was discussed (Hodgson and Rose, 2007).

Organic Solvents

There was one new report on the effects of aerosolized vapor of jet fuel on rats. Rats exposed for 4 weeks showed changes in stool and urine output, increased brain dopamine release and metabolism, and in rearing and hyperaroused behavior (Baldwin et al., 2007).

C. Immune Dysfunction and Infectious Diseases

The U.S. Department of Defense initiated the Anthrax Vaccine Immunization Program in 1998. There has been concern that anthrax vaccination could result in increased risk to members of the military population. Two studies completed in 2007demonstrated that immunization data and anthrax adverse-event reporting were highly consistent in the Defense Medical Surveillance System (DMSS) and Vaccine Adverse Event Reporting System (VAERS) systems (McNeil et al., 2007; Payne et al., 2007). Electronic vaccine records and the Medical Outcomes Study 36-Item Short Form Health Survey for Veterans (SF-36V) were used by Smith and coworkers to evaluate the possibility of association between anthrax vaccination and adverse health outcome data. They concluded that there were no differences between vaccinated and unvaccinated service personnel in overall measures of health (Smith et al., 2007).

Rheumatologic symptoms including joint pain and stiffness have been proposed to be involved in Gulf War veterans' illness (GWVI), perhaps as a part of generalized immune dysfunction. In a 2007 study, investigators obtained synovial tissue from the joints of individuals with GWVI who had joint pain, and compared it with synovial tissue from clinically asymptomatic controls and patients with rheumatoid arthritis and osteoarthritis. Indications of inflammation were seen in patients with both types of arthritis, but tissue from individuals with GWVI did not differ from those of normal controls. Results from this study agree with other studies that did not document immunologic abnormalities associated with GWVI (Diaz-Torne et al., 2007).

D. Reproductive Health

Kelsall and co-workers examined the effects that deployment in the 1991 Gulf War had on the reproductive health of male Australian Gulf War veterans and a military comparison group, using a mail questionnaire. The two groups reported similar rates of pregnancies and live births. There was no effect seen on the risk of miscarriage, stillbirth, premature birth, low birth weight, or having a birth defect or chromosomal abnormality. Their conclusion was that the data did not show increased risk of adverse reproductive outcome in Australian Gulf War veterans (Kelsall et al., 2007).

E. Symptoms and General Health

A review of symptoms associated with Gulf War service was presented by Iversen and colleagues that recommends research on effective interventions (Iversen et al., 2007). In a population of UK military personnel, a mail survey was conducted showing disabled Gulf War veterans were more likely overweight and hypertensive but no other differences in medical conditions were evident when Gulf War veterans with physical disability were compared to non-Gulf veterans with similar physical disability (Ismail et al., 2007). Military personnel deployed to the Gulf War were more likely to use emergency department services than non-deployed five years post deployment, with National Guard and Reserve most likely to be hospitalized (Helmer et al., 2007). LaDou suggested that circadian dysrhythmia may be related to the persistent symptoms in veterans with Gulf War illnesses (LaDou, 2007).

Chronic fatigue syndrome (CFS), multiple chemical sensitivity (MCS), and fibromyalgia (FM) commonly co-occur. Some propose that CFS, MCS, and FM are manifestations of the same illness based on high rates of co-occurrence and overlapping diagnostic criteria. Although the exact role of the hypothalamo-pituitary-adrenal (HPA) axis in stress-related disorders such as chronic fatigue syndrome (CFS), fibromyalgia syndrome (FMS), chronic pelvic pain, and post-traumatic stress disorder not clear, these conditions are often characterized by alterations in HPA axis activity (Tanriverdi et al., 2007). There may be some overlap in patient populations in the reports presented below.

Chronic Pain

UK Gulf War veterans reported pain in more body areas when compared with Bosnia and era comparison group (Stimpson et al., 2006). Sharma and co-workers presented a review of treatment possibilities for complex regional pain syndrome (Sharma et al., 2006). Chronic pain is often reported with CFS, which was examined by Knoop and colleagues specifically to determine whether Cognitive Behavioral Therapy (CBT) could also reduce pain severity ratings. Adult and adolescent CFS patients showed reduced pain severity and locations predicted by the decrease in fatigue (Knoop et al., 2007b). Alexander and colleaguescompared cerebrospinal fluid (CSF) levels of pro- and anti-inflammatory cytokines, chemokines and several biochemical factors in patients afflicted with Complex Regional Pain Syndrome (CRPS) to levels found in patients suffering with other non-painful or painful conditions. There was no elevation or reduction of a CSF marker that was specific for CRPS patients but other patterns of markers were suggested that could be helpful in both elucidating the mechanisms involved in the disease process and supporting the diagnosis of CRPS (Alexander et al., 2007). McBeth and co-workers found that HPA axis dysfunction could distinguish patients who will develop chronic widespread pain based on a psychosocial profile and salivary cortisol measures (McBeth et al., 2007).

Forman-Hoffman and colleagues compared the prevalence of chronic widespread pain (CWP) between deployed and nondeployed veterans five years after PGWI in a cross-sectional study of veterans and found 16% of 3695 veterans interviewed had CWP. Gulf deployment was associated with higher prevalence of CWP than deployment elsewhere after adjustment. Both deployed and nondeployed veterans with CWP reported more health care utilization and co-morbidities and lower health-related quality of life scores than veterans without CWP (Forman-Hoffman et al., 2007).

Fibromyalgia

Fibromyalgia (FM) is a chronic rheumatologic condition characterized by generalized pain and fatigue, and was reviewed generally (Clauw, 2007) as well as its specific relation to growth hormone (Jones et al., 2007b). Another review presented in 2007 by Kim examined skin biopsy samples for peripheral changes as a possible future diagnostic (Kim, 2007). An internet survey questionnaire was developed by the National Fibromyalgia Association (NFA) in conjunction with a task force of "experts in the field" was completed by 2,569 people provides a snap-shot of FM as reported by a self-selected population of people (Bennett et al., 2007). This descriptive data has a heuristic function, in that it identifies several issues for further research, such as the prescribing habits of FM health care providers, the role of emotional precipitants, the impact of obesity, the significance of low back pain and the nature of FM related stiffness. Brown and Jason examined the diagnoses of CFS, MCS, and FM by comparing individuals with one or more illness on functioning, psychiatric comorbidity, coping style, and in vivo physical measures. Individuals with CFS alone were the highest functioning group across several domains, such as disability, depression, and severity of symptoms while participants with three diagnoses experienced the greatest amount of disability (Brown and Jason, 2007). In patients with FM, CSF corticotrophin-releasing factor (CRF) levels were different in women with FM and physical or sexual abuse history, and levels were associated with pain and altered autonomic function (McLean et al., 2006). In another

study, increased sensitivity to glucocorticoid feedback in FM, with more pronounced suppression of cortisol but not ACTH, was observed (Wingenfeld et al., 2007). When performing a stressful task, FM patients show abnormal cardiovascular responses (Nilsen et al., 2007). FM patients reportedly showed an abnormal dopamine response to pain when subjected to deep muscle pain via injection into the anterior tibialis muscle (Wood et al., 2007).

Several FM treatment trials were conducted in 2007 that assessed the efficacy and safety of gabapentin in patients with fibromyalgia in a 12-week, randomized, double-blind study (Arnold et al., 2007). Gabapentin-treated patients displayed a significantly greater improvement in average pain severity score as well as other measures but not on mean point tender pain threshold; gabapentin was generally well tolerated. Paroxetine controlled release appeared to improve FM symptomatology but not pain measures (Patkar et al., 2007). Babu and co-workers conducted a randomized controlled trial involving two groups of FM patients, one receiving electromyography biofeedback and the other a sham biofeedback and reported biofeedback as a treatment modality reduced pain in FM patients, along with improvements in the number of tender points (Babu et al., 2007). Hassett and colleagues examined the effect of heart rate variability biofeedback on FM in a small number of women and showed potential benefit especially related to heart rate in those with FM (Hassett et al., 2007). Mayhew and Ernst reviewed clinical trial literature and reported that acupuncture did not appear to be effective as a symptomatic treatment for FM (Mayhew and Ernst, 2007). Maquet and colleagues reviewed the results of studies with exercise therapy and found a beneficial effect for CFS patients with pain or fatigue (Maquet et al., 2007).

Laske and co-workers reported that serum concentrations of brain derived nerve growth factor level in FM patients differed from that of healthy controls, suggesting a nociceptive mechanism for pain in FM (Laske et al., 2007). Bazzichi and colleagues examined the possible role of the soluble factor in FM by studying the correlation of cytokine levels with the patients' clinical and psychiatric profile and reported higher levels of cytokines in FM patients (Bazzichi et al., 2007).

Chronic Fatigue Syndrome (CFS)

A 2007 telephone survey estimated that 2.54% of 18-59 year olds suffer from CFS in Georgia (Reeves et al., 2007). Komaroff presented the theory that human herpesvirus-6 (HHV6) may trigger CFS in a subset of patients because it is associated with many CFS patient findings (Komaroff, 2006). Faulkner and Smith aimed to replicate and extend the finding that chronic fatigue syndrome (CFS) patients report increased susceptibility to upper respiratory tract illnesses (URTIs) when compared with healthy volunteers by investigating the role of psychological distress (stress and negative mood) in the recurrence of URTIs in CFS patients. CFS patients reported more URTIs than the controls with stress scores (and negative mood) were significantly higher in the week prior to the occurrence of URTIs than in weeks when no subsequent illness occurred. High levels of stress were also associated with greater subsequent fatigue (Faulkner and Smith, 2006). Newton and co-workers conducted a cross-sectional study of CFS patients and controls that suggested the Composite Autonomic Symptom Scale is a valid diagnostic criterion for autonomic dysfunction in CFS, and can be used to identify patients for targeted intervention studies (Newton et al., 2007). CFS patients showed urinary excretion and blood parameter anomalies supportive of homeostatic alterations (Niblett et al., 2007). Oxidative damage in erythrocytes was also reported in CFS patients (Richards et al., 2007).

Goldenberg reviewed pharmacological treatment for FM (Goldenberg, 2007). One study assessed the efficacy of the atypical neuroleptic olanzapine for the treatment of fibromyalgia symptoms by chart review of 51 patients (Freedenfeld et al., 2006). Post-treatment ratings on the same scales revealed significant improvement on virtually all scales. The benefits of olanzapine to improve fibromyalgia symptoms must, however, be carefully considered because there were a variety of side effects (i.e., weight gain, somnolence/sedation) that were of sufficient strength to cause a number of patients to discontinue treatment. Acclydine was not found to be beneficial for the treatment of CFS (The et al., 2007).

Guo reported that acupuncture plus mugwort therapy, combined with a psychological approach, is an effective therapy for CFS; 88.7% off 310 cases observed were cured, 9% improved, and 7 cases failed treatment (Guo, 2007). Although not treatment trials, Maes and co-workers reported that NF-κ-β production related to symptoms in CFS (Maes et al., 2007a) and that COX2 and iNOS relationship, proposed an inflammatory response in CFS that might be treatable with NF-κ-β, COX2 and iNOS inhibitors (Maes et al., 2007b). Mihaylova and colleagues reported that patients with CFS are deficient in T- and natural killer cell activation, perhaps due to early activation of the immune system (Mihaylova et al., 2007). An assessment of the effect of exercise in CFS patients found that physical symptoms worsened while other measures, such as cognitive function, did not (Yoshiuchi et al., 2007).

The involvement of brain interferon-α and serotonin transporter was reported in an immunologically induced fatigue model in rats, lending support to CNS involvement over muscle fatigue (Katafuchi et al., 2006).

F. Abstracts from Published Research

Alexander GM, Perreault MJ, Reichenberger ER, Schwartzman RJ (2007) Changes in immune and glial markers in the CSF of patients with Complex Regional Pain Syndrome. Brain Behav Immun 21:668-676.
Abstract: Complex Regional Pain Syndrome is a severe chronic pain condition characterized by sensory, autonomic, motor and dystrophic signs and symptoms. The pain in CRPS is continuous, it worsens over time, and it is usually disproportionate to the severity and duration of the inciting event. This study compares cerebrospinal fluid (CSF) levels of pro- and anti-inflammatory cytokines, chemokines and several biochemical factors (glial fibrillary acidic protein (GFAP), the nitric oxide metabolites (nitrate plus nitrite), the excitatory amino acid neurotransmitter glutamate, calcium, total protein and glucose) in patients afflicted with CRPS to levels found in patients suffering with other non-painful or painful conditions. The aim of the study is to determine the degree of involvement of glial cells and immune system mediators in the pathophysiology of CRPS. There was no elevation or reduction of a CSF marker that was specific for CRPS patients. However, there were several patterns of markers that could be helpful in both elucidating the mechanisms involved in the disease process and supporting the diagnosis of CRPS. The most common pattern was found in 50% (11 out of 22) of the CRPS patients and consisted of; elevated IL-6, low levels of IL-4 or IL-10, increased GFAP or MCP1 and increases in at least two of the following markers NO metabolites, calcium or glutamate. The results from this and other similar studies may aid in elucidating the mechanisms involved in the pathophysiology of CRPS. A better understanding of these mechanisms may lead to novel treatments for this very severe, life-altering illness

Arfsten DP, Wilfong ER, Bekkedal MY, Johnson EW, McInturf SM, Eggers JS, Schaeffer DJ, Still KR (2007) Evaluation of the effect of implanted depleted uranium (DU) on adult rat behavior and toxicological endpoints. J Toxicol Environ Health A 70:1995-2010.
Abstract: In 2002, the Naval Health Research Center Toxicology Detachment began a study to determine the effects of surgically implanted depleted uranium (DU) pellets on adult rat (e.g., P1 generation) health and reproduction. In this report, the effect of implanted DU on adult rat behavior and health is described. Adult Sprague-Dawley (SD) rats, 8 wk of age, were surgically implanted with 0, 4, 8, 12, or 20 DU pellets (1 x 2 mm); 20 DU pellets of size 1 x 2 mm approximates to 0.22 kg (0.5 lb) of DU in a 70-kg (154 lb) person. Control animals were implanted with 12 or 20 tantallum (Ta) pellets. The animals were then housed for up to 150 d postimplantation or 20% of an assumed 2-yr life span for rats. The concentration of uranium in urine directly correlated with the number of implanted DU pellets, indicating that DU was migrating into the body from the implanted pellets. Three male and 4 female animals died during the 150-d period of causes apparently not related to DU implantation. Behavioral testing found no definitive evidence of neurobehavioral perturbations associated with DU implantation. Uranium translocated to tissues known to sequester uranium (bone, teeth, and kidneys), but uranium concentrations varied considerably within each dose group and did not follow a dose-response pattern as anticipated. Serum chemistry values were within normal ranges for the SD rat. However, alanine aminotransferase measurements were significantly lower for rats implanted with 20 DU pellets as compared to sham surgery controls but not when compared to animals implanted with Ta pellets only. Phosphate measurements were significantly lower for female rats implanted with 20 DU pellets as compared to both sham surgery controls and animals implanted with Ta pellets only. Monocyte ratios were higher in adult rats implanted with 20 DU pellets as compared to sham surgery controls but not when compared to animals implanted with 20 Ta pellets. Mean platelet volume was found to be significantly lower for rats implanted with 20 DU pellets as compared to sham surgery controls but not when compared to animals implanted with 20 Ta pellets. Gross necropsy found no obvious tissue abnormalities in implanted rats, and the weights of major tissues did not differ between Ta- and DU-implanted animals. Histopathologic analysis of major tissues from animals implanted with 0 pellets, 20 Ta pellets, or 20 DU pellets found no differences between treatment groups. The findings of this study indicate that implantation of up to 20 DU pellets in adult rats did not have a significant negative impact on their general health and neurobehavioral capacities when assessed after 150 d of pellet implantation. However, the growing body of data on the potential health effects associated with DU exposure warrants further studies involving higher embedded DU body burdens in conjunction with longer surveillance periods postimplantation

Arnold LM, Goldenberg DL, Stanford SB, Lalonde JK, Sandhu HS, Keck PE, Jr., Welge JA, Bishop F, Stanford KE, Hess EV, Hudson JI (2007) Gabapentin in the treatment of fibromyalgia: a randomized, double-blind, placebo-controlled, multicenter trial. Arthritis Rheum 56:1336-1344.

Abstract: OBJECTIVE: To assess the efficacy and safety of gabapentin in patients with fibromyalgia. METHODS: A 12-week, randomized, double-blind study was designed to compare gabapentin (1,200-2,400 mg/day) (n=75 patients) with placebo (n=75 patients) for efficacy and safety in treating pain associated with fibromyalgia. The primary outcome measure was the Brief Pain Inventory (BPI) average pain severity score (range 0-10, where 0=no pain and 10=pain as bad as you can imagine). Response to treatment was defined as a reduction of >or=30% in this score. The primary analysis of efficacy for continuous variables was a longitudinal analysis of the intent-to-treat sample, with treatment-by-time interaction as the measure of effect. RESULTS: Gabapentin-treated patients displayed a significantly greater improvement in the BPI average pain severity score (P=0.015; estimated difference between groups at week 12=-0.92 [95% confidence interval -1.75, -0.71]). A significantly greater proportion of gabapentin-treated patients compared with placebo-treated patients achieved response at end point (51% versus 31%; P=0.014). Gabapentin compared with placebo also significantly improved the BPI average pain interference score, the Fibromyalgia Impact Questionnaire total score, the Clinical Global Impression of Severity, the Patient Global Impression of Improvement, the Medical Outcomes Study (MOS) Sleep Problems Index, and the MOS Short Form 36 vitality score, but not the mean tender point pain threshold or the Montgomery Asberg Depression Rating Scale. Gabapentin was generally well tolerated. CONCLUSION: Gabapentin (1,200-2,400 mg/day) is safe and efficacious for the treatment of pain and other symptoms associated with fibromyalgia

Babu AS, Mathew E, Danda D, Prakash H (2007) Management of patients with fibromyalgia using biofeedback: a randomized control trial. Indian J Med Sci 61:455-461.

Abstract: OBJECTIVE: Fibromyalgia syndrome (FMS) is a chronic rheumatological condition which could be characterized by generalized pain and fatigue. Cognitive and behavioral therapy has been found to be a suitable technique in the management of FMS. This study intends to evaluate the efficacy of electromyography (EMG) biofeedback to reduce pain in patients with FMS. MATERIALS AND METHODS: A randomized controlled trial involving two groups of FMS patients, one receiving electromyography (EMG) biofeedback and the other a sham biofeedback, was carried out. The assessment tools included in the study were fibromyalgia impact questionnaire (FIQ), visual analogue scale (VAS), six-minute walk test (SMWT) and number of tender points; and tenderness of each tender point was done for both the groups. STATISTICS: A Student's 't' test was used to study the test for significance. RESULTS: After using biofeedback, the mean VAS scores and the mean number of tender points were found to be 3 out of 10 and 6 out of 18 respectively. Subjective analysis from both groups showed improvement in physical and psychological realms. Statistical significance. CONCLUSION: Biofeedback as a treatment modality reduces pain in patients with FMS, along with improvements in FIQ, SMWT and the number of tender points

Baireddy P, Mirajkar N, Nallapaneni A, Singleton N, Pope CN (2007) Effects of combined, multiple stressors on pyridostigmine-induced acute toxicity in rats. Arch Toxicol 81:283-289.

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

Baldwin CM, Figueredo AJ, Wright LS, Wong SS, Witten ML (2007) Repeated aerosol-vapor JP-8 jet fuel exposure affects neurobehavior and neurotransmitter levels in a rat model. J Toxicol Environ Health A 70:1203-1213.

Abstract: Four groups of Fischer Brown Norway hybrid rats were exposed for 5, 10, 15, or 20 d to aerosolized-vapor jet propulsion fuel 8 (JP-8) compared to freely moving (5 and 10-d exposures) or sham-confined controls (15 and 20-d exposures). Behavioral testing utilized the U.S. Environmental Protection Agency Functional Observational Battery. Exploratory ethological factor analysis identified three salient factors (central nervous system [CNS] excitability, autonomic 1, and autonomic 2) for use in profiling JP-8 exposure in future studies. The factors were used as dependent variables in general linear modeling. Exposed animals were found to engage in more rearing and hyperaroused behavior compared to controls, replicating prior JP-8 exposure findings. Exposed animals also showed increasing but rapidly decelerating stool output (autonomic 1), and a significant increasing linear trend for urine output (autonomic 2). No significant trends were noted for either of the control groups for the autonomic factors. Rats from each of the groups for each of the time frames were randomly selected for tissue assay from seven brain regions for neurotransmitter levels. Hippocampal DOPAC was significantly elevated after 4-wk JP-8 exposure compared to both control groups, suggesting increased dopamine release and metabolism. Findings indicate that behavioral changes do not appear to manifest until wk 3 and 4 of exposure, suggesting the need for longitudinal studies to determine if these behaviors occur due to cumulative exposure, or due to behavioral sensitization related to repeated exposure to aerosolized-vapor JP-8

Barber DS, Hancock SK, McNally AM, Hinckley J, Binder E, Zimmerman K, Ehrich MF, Jortner BS (2007) Neurological effects of acute uranium exposure with and without stress. Neurotoxicology 28:1110-1119.

Abstract: Circulating uranium rapidly enters the brain and may cause adverse effects on the nervous system that are potentially modulated by stress. In this study, the neurological effects of a single intramuscular injection of 0, 0.1, 0.3, or 1 mg uranium/kg (as uranyl acetate, UA) in rats were examined in the presence and absence of stress. Treatment with UA produced time and dose-dependent increases in serum and regional brain uranium levels. While serum levels returned to control levels by day 30, brain levels remained elevated. Application of stress did not affect the distribution or retention of uranium. Exposure to 1 mg U/kg significantly decreased ambulatory activity, weight gain, forelimb grip strength and transiently impaired working memory. Effects on grip strength and memory were prevented by application of stress prior to uranium exposure. Striatal dopamine content was reduced by 30% 3 days after treatment with 1mg/kg (59+/-6 nmol/mg tissue versus 41+/-5 nmol/mg tissue), but levels returned to control 7 days after uranium exposure. The effect on dopamine was ameliorated by prior application of stress. Exposure to UA did not alter 3,4 dihydroxyphenylacetic acid (DOPAC) levels or numbers of D2 receptors in the striatum. No effect of uranium or stress was observed on levels of GABA, serotonin, norepinephrine, or glutathione (GSH) in the striatum, hippocampus, cerebellum, or cortex. These results indicate that single intramuscular exposures to uranium produce sustained elevation of brain uranium levels and at doses above 0.3 mg/kg can have adverse neurological effects. Application of stress prior to uranium administration modulates neurological effects, but the mechanism is not due to effects on uranium distribution. Uranium exposure also produced renal toxicity which must be considered to accurately assess the effects of uranium on neurological function

Barillet S, Adam C, Palluel O, Devaux A (2007) Bioaccumulation, oxidative stress, and neurotoxicity in Danio rerio exposed to different isotopic compositions of uranium. Environ Toxicol Chem 26:497-505.

Abstract: Experiments were carried out on adult male zebrafish (Danio rerio) to assess early changes induced by waterborne exposure to different isotopic compositions of uranium (depleted uranium associated or not with 233U). Oxidative stress and neurotoxicity were selected as effect endpoints to characterize uranium chemo- and radiotoxicity. Catalase, glutathione peroxidase, and superoxide dismutase activities and total glutathione content of hepatic extracts, as well as brain acetylcholinesterase activity and uranium bioaccumulation, were measured. Oxidative stress induced by uranium exposure led to decreases in superoxide dismutase and catalase activity levels as well as total glutathione content in liver extracts. These perturbations were significantly more marked in 233U-exposed fish. Furthermore, significant increase in acetylcholinesterase activity was observed in brain extracts at the same level, whatever the isotopic composition of uranium

Barrash J, Denburg NL, Moser DJ, Woolson RF, Schumacher AJ, Doebbeling BN (2007) Credibility of neuropsychological performances of Persian Gulf War veterans and military control subjects participating in clinical epidemiological research. Mil Med 172:697-707.
Abstract: We investigated whether Persian Gulf War veterans (GWVs) were more likely than Persian Gulf War-era veterans deployed elsewhere (GEVs) to have noncredible neuropsychological examinations. A total of 301 GWVs and 99 GEVs underwent neuropsychological testing. The credibility of 173 examinations showing impairment was evaluated based on test performances, clinical background, psychometric measures, and other self-report data. All 11 examinations judged less than fully credible by one neuropsychologist, plus 19 examinations judged impaired but credible, were then evaluated independently by two more neuropsychologists. Noncredibility was judged with excellent reliability (93% agreement). Seven examinations were judged noncredible. Rates of noncredibility did not differ between GWVs (1%) and GEVs (4%). The pattern of associations of noncredible examinations with cognitive, psychological, and clinical variables generally indicated defective neuropsychological scores, with no coherent pattern, and personality disorder. Findings supported the validity of noncredibility judgments and suggested that noncredible examinations are not a significant problem in neuropsychological investigations of GWVs

Bazzichi L, Rossi A, Massimetti G, Giannaccini G, Giuliano T, De FF, Ciapparelli A, Dell'Osso L, Bombardieri S (2007) Cytokine patterns in fibromyalgia and their correlation with clinical manifestations. Clin Exp Rheumatol 25:225-230.
Abstract: OBJECTIVE: To examine the possible role of the soluble factor in fibromyalgia (FM) by studying the correlation of cytokine levels with the patients' clinical and psychiatric profile. METHODS: Eighty FM patients underwent clinical and psychiatric evaluations, and plasma levels of cytokines (IL-1, IL-6, IL-8, IL-10, TNF-α), a specific marker of inflammation, rheumatoid factor (RF), anti-extractable nuclear antigen (ENA) antibodies, and anti-nuclear factor (FAN) were measured. RESULTS: Higher levels of IL-10, IL-8 and TNFα were found in FM patients than in controls. Significant correlations between the biochemical parameters and clinical data were found. CONCLUSION: The higher levels of cytokines found in FM patients suggest the presence of an inflammatory response system (IRS) and highlight a parallel between the clinical symptoms and biochemical data. They support the hypothesis that cytokines may play a role in the clinical features of fibromyalgia. In addition, the similar cytokine patterns found in FM patients with different psychiatric profiles suggests that IRS impairment may play a specific role in the disease

Bennett RM, Jones J, Turk DC, Russell IJ, Matallana L (2007) An internet survey of 2,596 people with fibromyalgia. BMC Musculoskelet Disord 8:27.
Abstract: BACKGROUND: This study explored the feasibility of using an Internet survey of people with fibromyalgia (FM), with a view to providing information on demographics, sources of information, symptoms, functionality, perceived aggravating factors, perceived triggering events, health care utilization, management strategies, and medication use. METHODS: A survey questionnaire was developed by the National Fibromyalgia Association (NFA) in conjunction with a task force of "experts in the field". The questionnaire underwent several rounds of testing to improve its face validity, content validity, clarity and readability before it was mounted on the internet. The questionnaire consisted of 121 items and is available online at the website of the National Fibromyalgia Association. RESULTS: The questionnaire was completed by 2,569 people. Most were from the United States, with at least one respondent from each of the 50 states. Respondents were predominantly middle-aged Caucasian females, most of whom had FM symptoms for > or = 4 years. The most common problems were morning stiffness, fatigue, nonrestorative sleep, pain, concentration, and memory. Aggravating factors included: emotional distress, weather changes, insomnia, and strenuous activity. Respondents rated the most effective management modalities as rest, heat, pain medications, antidepressants, and hypnotics. The most commonly used medications were: acetaminophen, ibuprofen, naproxen, cyclobenzaprine, amitriptyline, and aspirin. The medications perceived to be the most effective were: hydrocodone preparations, aprazolam, oxycodone preparations, zolpidem, cyclobenzaprine, and clonazepam. CONCLUSION: This survey provides a snap-shot of FM at the end of 2005, as reported by a self-selected population of people. This descriptive data has a heuristic function, in that it identifies several issues for further research, such as the prescribing habits of FM health care providers, the role of emotional precipitants, the impact of obesity, the significance of low back pain and the nature of FM related stiffness

Brown MM, Jason LA (2007) Functioning in individuals with chronic fatigue syndrome: increased impairment with co-occurring multiple chemical sensitivity and fibromyalgia. Dyn Med 6:6.
Abstract: BACKGROUND: Chronic fatigue syndrome (CFS), multiple chemical sensitivity (MCS), and fibromyalgia (FM) commonly co-occur. Some propose that CFS, MCS, and FM are manifestations of the same illness based on high rates of co-occurrence and overlapping diagnostic criteria. This study seeks to differentiate these diagnoses by

comparing individuals with one or more illness on functioning, psychiatric comorbidity, coping style, and in vivo physical measures. METHODS: Participants included 114 men and women who met criteria for CFS. FM was diagnosed during a physical examination, and MCS was assessed using a questionnaire. Participants were divided into four groups: CFS alone, CFS-MCS, CFS-FM, and CFS-MCS-FM. Self-report measures, a psychiatric interview, and in vivo physical measures were given. RESULTS: 43.9% met criteria for CFS alone, 23.7% met criteria for CFS-MCS, 15.8% met criteria for CFS-FM, and 16.7% met criteria for CFS-MCS-FM. The CFS-MCS-FM group was more disabled than the CFS alone group on measures of physical functioning, general health, and bodily pain. In vivo measures did not differ, but the CFS-MCS-FM group rated exertion higher than the CFS alone group. CONCLUSION: Individuals with CFS alone were the highest functioning group across several domains, such as disability, depression, and severity of symptoms. Participants with three diagnoses experienced the greatest amount of disability. While substantial co-occurrence of these illnesses was found, this study provides evidence that having more than one illness exacerbates one's disability beyond CFS alone

Clauw DJ (2007) Fibromyalgia: update on mechanisms and management. J Clin Rheumatol 13:102-109.
Summary: Chronic pain and fatigue syndromes such as fibromyalgia represent a part of a clinical spectrum of overlapping disorders that afflict a significant portion of the general proportion. Data suggest that there is a familial tendency to develop these disorders, and that exposure to physical, emotional, or environmental stressors' may trigger the initiation of symptoms. Once the illness develops, the majority of the symptoms are likely mediated by central nervous system mechanisms. Management strategies are similar to other chronic illnesses, where empathetic health care providers should develop a partnership with their patients. At one end of the continuum, there are some individuals with fibromyalgia that respond to a single medication or a graded, low-impact exercise program. At the other end of the continuum is the tertiary care patient with high levels of distress who has no sense of control of their illness, little social support, and has looked toward disability and compensation systems to try to solve their problem. For this individual, and many in between, multimodal programs that integrate nonpharmacological (especially exercise, CBT) and pharmacological therapies are required.

Claypoole KH, Noonan C, Mahurin RK, Goldberg J, Erickson T, Buchwald D (2007) A twin study of cognitive function in chronic fatigue syndrome: the effects of sudden illness onset. Neuropsychology 21:507-513.
Abstract: Variable reports of neuropsychological deficits in individuals with chronic fatigue syndrome (CFS) may, in part, be attributable to methodological limitations. In this study, these limitations were addressed by controlling for genetic and environmental influences and by assessing the effects of comorbid depression and mode of illness onset. Specifically, the researchers conducted a co-twin control study of 22 pairs of monozygotic twins, in which 1 twin met strict criteria for CFS and the co-twin was healthy. Twins underwent a structured psychiatric interview and comprehensive neuropsychological assessment evaluating 6 cognitive domains. Results indicated that twin groups had similar intellectual and visual memory functioning, but fatigued twins exhibited decreases in motor functions ($p = .05$), speed of information processing ($p = .02$), verbal memory ($p = .02$), and executive functioning ($p = .01$). Major depression did not affect neuropsychological functioning among fatigued twins, although twins with sudden illness onset demonstrated slowed information processing compared with those with gradual onset ($p = .01$). Sudden onset CFS was associated with reduced speed of information processing. If confirmed, these findings suggest the need to distinguish illness onset in future CFS studies and may have implications for treatment, cognitive rehabilitation, and disability determination

Concato J, Aslan M, Palmisano MM, Doebbeling CC, Peduzzi P, Ofek K, Soreq H, Doebbeling B (2007) Acetylcholinesterase activity in veterans of the first gulf war. J Investig Med 55:360-367.
Abstract: Background: Factors affecting acetylcholine-mediated neurotransmission have been proposed as possible explanations for physical and mental health symptoms among veterans of the 1990-1991 Gulf War. This study was designed to examine relationships of deployment to the Gulf, as well as symptoms after military service, with postdeployment activity of acetylcholinesterase (AChE) and related enzymes. Methods: The patient population included 488 veterans, originally from Iowa at enlistment, who served in the US military during August 1990 to July 1991. Demographic, military, and clinical characteristics were obtained from a population-based cohort study (in 1995-1996) and from a nested case-control study (in 1999-2002). Stored serum samples (from the 1999-2002 assessment) were analyzed for activity of AChE and related enzymes. These two data sources were merged, and multiple linear regression models estimated the association of deployment, stress (anxiety) or mood disorders, and symptoms compatible with Gulf War veterans' illnesses (GWVIs), with enzyme activity. Results: Seventy-four percent ($n = 361$) of veterans had been deployed to the Gulf. At the time of evaluation, 23% ($n = 113$) of participants reported anxiety and 15% ($n = 71$) reported mood disorders; 49% ($n = 171$ of 347 eligible veterans) had symptoms of GWVIs, and the

median AChE activity was 839 units. AChE activity was similar for compared groups across all categories, including an adjusted difference of -27 units (p = .50) for deployed versus nondeployed veterans and 87 units (p = .13) for veterans with versus without symptoms of GWVIs. Conclusions: Neither deployment to the Gulf nor symptoms compatible with GWVIs are associated with long-term serum AChE activity

Cook DB, O'Connor PJ, Lange G, Steffener J (2007) Functional neuroimaging correlates of mental fatigue induced by cognition among chronic fatigue syndrome patients and controls. Neuroimage 36:108-122.
Abstract: The neural mechanisms underlying feelings of fatigue are poorly understood. The primary purpose of the study was to use functional magnetic resonance imaging (fMRI) to determine the association between feelings of mental fatigue and blood oxygen level dependent (BOLD) brain responses during a mentally fatiguing cognitive task. Healthy, non-fatigued controls and chronic fatigue syndrome (CFS) patients were included to determine the influence of chronic levels of fatigue on brain responses. We hypothesized that mental fatigue would be significantly related to brain activity during a fatiguing cognitive task but not during either a non-fatiguing motor (finger tapping) or cognitive (auditory monitoring) task. Patients (n=9) and controls (n=11) completed a finger tapping task, a simple auditory monitoring task and a challenging working memory task, designed to induce mental fatigue, while undergoing fMRI. Fatigue was measured prior to scanning and following each task during fMRI data collection. Results showed that mental fatigue was significantly related to brain activity during the fatiguing cognitive task but not the finger tapping or simple auditory monitoring tasks. Significant (p< or =0.005) positive relationships were found for cerebellar, temporal, cingulate and frontal regions. A significant (p=0.001) negative relationship was found for the left posterior parietal cortex. CFS participants did not differ from controls for either finger tapping or auditory monitoring tasks, but exhibited significantly greater activity in several cortical and subcortical regions during the fatiguing cognitive task. Our results suggest an association between subjective feelings of mental fatigue and brain responses during fatiguing cognition

Cook DB, Stegner AJ, McLoughlin MJ (2007) Imaging pain of fibromyalgia. Curr Pain Headache Rep 11:190-200.
Abstract: Brain imaging studies have provided objective evidence of abnormal central regulation of pain in fibromyalgia (FM). Resting brain blood flow studies have reported mixed findings for several brain regions, whereas decreased thalamic blood flow has been noted by several investigators. Studies examining the function of the nociceptive system in FM have reported augmented brain responses to both painful and non-painful stimuli that may be influenced by psychologic dispositions such as depressed mood and catastrophizing. Treatment approaches are beginning to demonstrate the potential for brain imaging to improve our understanding of pain-alleviating mechanisms. Data from other chronic conditions suggest that idiopathic pain may be maintained by similar central abnormalities as in FM, whereas chronic pain conditions with a known nociceptive source may not be. Future neuroimaging research in FM is clearly warranted and should continue to improve our understanding of factors involved in pain maintenance and symptom exacerbation

Dave JR, Connors RA, Genovese RF, Whipple RA, Chen RW, DeFord SM, Moran AV, Tortella EC (2007) DNA fragmentation in leukocytes following repeated low dose sarin exposure in guinea pigs. Cell Mol Life Sci 64:2823-2828.
Abstract: The objective of this study was to determine levels of DNA fragmentation in blood leukocytes and parietal cortex from guinea pigs following repeated low-level exposure to the chemical warfare nerve agent (CWNA) sarin. Guinea pigs were injected (s.c.) once a day for 10 days with saline, or 0.1, 0.2, or 0.4 LD50 (50% mean lethal dose) sarin dissolved in sterile physiological saline. Blood and parietal cortex was collected after injection at 0, 3, and 17 days recovery and evaluated for DNA fragmentation using single-cell gel electrophoresis (Comet assay). Cells were imaged using comet analysis software and three parameters of DNA fragmentation measured: tail length, percent DNA in the tail, and tail moment arm. Repeated low-dose exposure to sarin produced a dose-dependent response in leukocytes at 0 and 3 days post-exposure. There was a significant increase in all measures of DNA fragmentation at 0.2 and 0.4 LD50, but not at 0.1 LD50. There was no significant increase in DNA fragmentation in any of the groups at 17 days post-exposure. Sarin did not produce a systematic dose-dependent response in parietal cortex at any of the time points. However, significant increases in DNA fragmentation at 0.1 and 0.4 LD50 were observed at 0 and 3 days post-exposure. All measures of DNA fragmentation in both leukocytes and neurons returned to control levels by 17 days post-exposure, indicating a small and non-persistent increase in DNA fragmentation following repeated low-level exposure to sarin

Diaz-Torne C, Schumacher HR, Yu X, Gomez-Vaquero C, Dai L, Chen LX, Clayburne G, Einhorn E, Sachdeva RM, Singh JA, Pessler F (2007) Absence of histologic evidence of synovitis in patients with Gulf War veterans' illness with joint pain. Arthritis Rheum 57:1316-1323.

Abstract: OBJECTIVE: An unexplained multisymptom illness, Gulf War veterans' illness (GWVI), has been described among allied force veterans of the first Gulf War (1990-1991). It has been proposed that some of its symptoms reflect an immune dysfunction, and rheumatologic symptoms including joint pain and stiffness are reported frequently. However, it is unknown whether synovial inflammation causes the articular symptoms. We examined synovial tissue from individuals with GWVI and joint pain for evidence of inflammation. METHODS: We compared synovial biopsy samples from 6 individuals with GWVI and joint pain with samples from 9 clinically asymptomatic controls (hematoxylin and eosin [H&E] stains only) and biopsy samples or surgically obtained specimens from 10 patients with rheumatoid arthritis (RA) and 12 with osteoarthritis (OA). Inflammatory changes were quantified in H&E stained sections with a modified synovitis score by immunostaining for CD3, CD20, CD38, CD68, Ki-67, and von Willebrand factor, and with a composite inflammation score based on these markers. RESULTS: Normal histology was seen in the GWVI specimens, except for mild focal lining hyperplasia and rare low-grade perivascular infiltrates in 1 specimen each. Mean +/- SEM synovitis scores were lowest and nearly identical in control (1.38 +/- 0.30) and GWVI specimens (1.41 +/- 0.29), intermediate in OA specimens (2.64 +/- 0.39), and highest in RA specimens (6.0 +/- 0.19). Likewise, inflammatory cells, cell division, vascular density, and composite inflammation score were lowest in the GWVI specimens. CONCLUSION: Despite significant joint pain, the GWVI synovia did not differ from normal controls. These results agree with other studies that have failed to document inflammatory or immunologic etiologies in GWVI

DiMartino L, Allen KD, Kasarskis E, Lindquist JH, Coffman CJ, Oddone EZ (2007) Characteristics associated with participation in DNA banking: The National Registry of Veterans with ALS. Contemp Clin Trials 28:572-582.

Abstract: OBJECTIVE: Characteristics that may influence participation in DNA banks are not well defined. The purpose of this study was to examine characteristics associated with participation in a DNA bank among veterans diagnosed with Amyotrophic Lateral Sclerosis (ALS). METHODS: Veterans who screened eligible for the National Registry of Veterans with ALS were initially contacted about the DNA Bank via telephone and then mailed a consent form. Registry participants were then categorized as consented for the DNA bank, actively refused, or passively refused (consent form not returned after >3 months and multiple reminders). The associations of consent status with age, gender, race, military branch, years of military service, VA health system use, and ALS Functional Rating Scale (ALSFRS) scores were examined. RESULTS: Registry participants (N=1020) were 98% male, 9.5% non-white, and the mean age was 64.1 years. 61.1% of participants were current VA health system users, and the branches of service were: Army (46.1%), Navy (22.1%), Air Force (23.2%), and Marines (8.3%). A total of 14.7% of Registry participants refused DNA banking (9.4% active refusal, 5.3% passive refusal). Results from multivariable models indicated participants who were non-White, VA users, or had lower ALSFRS scores (reflecting poorer function) had higher odds of refusal. Race and VA use were associated with active refusal, while age and ALSFRS score were associated with passive refusal. CONCLUSION: Although the overall refusal rate for DNA banking was relatively low, we still found important differences in consent by race, VA use, and functional status in this cohort of veterans with ALS. Because differential participation in DNA banking may influence generalizability, further efforts are needed to understand and intervene to reduce these differences

Doi H, Kikuchi H, Murai H, Kawano Y, Shigeto H, Ohyagi Y, Kira J (2006) Motor neuron disorder simulating ALS induced by chronic inhalation of pyrethroid insecticides. Neurology 67:1894-1895.

Abstract: Some agricultural chemicals are known to be neurotoxic. Pyrethroid insecticides are commonly used as they are highly toxic to a wide range of insects but have low toxicity to mammals. However, overexposure to pyrethroids can induce various neurotoxic symptoms such as numbness, seizure, tremor, and memory impairment.1 Such symptoms are usually transient, and there are no reports indicating that chronic intoxication from pyrethroid insecticides causes motor neuron damage, although a case of pathologically proven motor neuron death after acute massive ingestion of pesticides containing pyrethroids and organochlorine has been reported.2 Here, we report a case of slowly progressive motor neuron disease (MND) following chronic exposure to pyrethroids that was indistinguishable from ALS.

Dublineau I, Grandcolas L, Grison S, Baudelin C, Paquet F, Voisin P, Aigueperse J, Gourmelon P (2007) Modifications of inflammatory pathways in rat intestine following chronic ingestion of depleted uranium. Toxicol Sci 98:458-468.

Abstract: The environmental contamination by dispersion of depleted uranium (DU) might result in its chronic ingestion of DU by local populations. The aim of this study was to determine if chronic ingestion of DU at low doses induces inflammatory reactions in intestine, first biological system exposed to uranium after ingestion. Experiments were performed with rats receiving uranium in drinking water (40 mg/l) during 3, 6, or 9 months. Several parameters referring to prostaglandin, histamine, cytokine, and nitric oxide (NO) pathways were assessed in ileum. Concerning the prostaglandin pathway, a twofold increase in gene expression of cyclooxygenase of type 2 was noted after 6 months, with no changes in prostaglandins levels. At the same time, a decrease in mast cell number was observed without any changes in histamine levels. Experiments on cytokines showed increased gene expression of interleukin (IL)-1β and IL-10 at 6 months, and decreased messenger RNA level of CCL-2. This change was associated with decreased macrophage density. An opposite effect of DU was induced on neutrophils, since increased number was observed at 3 (x1.7) and 9 months (x3). The results obtained on NO pathway seemed to indicate that DU exposure inhibited this pathway (decreased endothelial NO synthase messenger RNA, inductive NO synthase activity and NO_2^-/NO_3^- levels) at 6 months. In conclusion, this study demonstrated that chronic ingestion of DU-induced time-dependent modifications of inflammatory pathways, notably in terms of immune cell content. The ultimate effects of DU contamination might be pathogenic by suppressing defense mechanisms or inducing hypersensitivity. Further experiments should be thus performed to determine real consequences on intestinal response to oral antigens

Dubovicky M, Paton S, Morris M, Mach M, Lucot JB (2007) Effects of combined exposure to pyridostigmine bromide and shaker stress on acoustic startle response, pre-pulse inhibition and open field behavior in mice. J Appl Toxicol 27:276-283.

Abstract: The present study investigated the effect of combined exposure of pyridostigmine bromide (PB) and chronic shaker stress on acoustic startle responses (ASR), pre-pulse inhibition (PPI) and open field behavior of adult C57BL/6J mice. PB (10 mg kg/1/day for 7 days) or saline was administered subcutaneously using osmotic Alzet minipumps implanted under the skin on the back of the mice. At the same time, the mice were exposed to 7 days of intermittent shaker stress. They were tested for ASR (100 dB and 120 dB stimuli) and PPI (70 dB + 100 dB and 70 dB + 120 dB) in the acoustic startle monitor system. The mice were assessed during the shaker stress on days 2 and 7 and 7, 14, 21 and 28 days after discontinuation of treatment. Separate groups of mice were tested in the open field in 15 min sessions on days 1, 3 and 6 during shaker stress and PB treatment. Exposure of mice to PB resulted in an exaggerated ASR, reduced PPI and non-significant decrease in locomotor activity. These behavioral changes were apparent only during exposure to PB. Repeated shaker stress did not have any effect on sensorimotor functions or open field behavior of mice. There was no prolonged or delayed effect of PB and/or stress on individual behavioral variables. The study found C57BL/6J mice to be behaviorally sensitive to PB treatment

Faulkner S, Smith A (2006) A longitudinal study of the relationship between psychological distress and recurrence of upper respiratory tract infections in chronic fatigue syndrome. Br J Health Psychol.

Abstract: Objectives: Previous research has found that chronic fatigue syndrome (CFS) patients report increased susceptibility to upper respiratory tract illnesses (URTIs) when compared with healthy volunteers. This study aimed to replicate and extend this research by investigating the role of psychological distress (stress and negative mood) in the recurrence of URTIs in CFS patients as well as its role in the recurrence of CFS symptoms. Design: A 15-week diary study. Methods: Measures of psychological stress, negative mood, recurrence of URTIs and symptoms were recorded each week for a 15-week period. CFS patients (N=21), who had been assessed and diagnosed according to the Oxford criteria, were recruited from the Cardiff Chronic Fatigue Clinic and compared with a matched group of healthy controls (N=18). Frequency of occurrence of infectious illness and the relationship between psychological stress/negative mood and occurrence of illness were assessed. Results: CFS patients reported more URTIs than the controls. Stress scores (and negative mood) were significantly higher in the week prior to the occurrence of URTIs than in weeks when no subsequent illness occurred. High levels of psychological stress also preceded the severity of reported symptoms of fatigue in the CFS group. Conclusions: CFS patients reported more frequent URTIs than healthy controls and these recurrences were preceded by high levels of psychological stress. High levels of stress were also associated with greater subsequent fatigue. Possible explanations of these results are discussed

Forman-Hoffman VL, Peloso PM, Black DW, Woolson RF, Letuchy EM, Doebbeling BN (2007) Chronic widespread pain in veterans of the first Gulf War: impact of deployment status and associated health effects. J Pain 8:954-961.

Abstract: Our study sought to 1) determine if deployment status is associated with chronic widespread pain (CWP), and 2) evaluate whether veterans with CWP have greater psychiatric comorbidity, higher health care utilization, and poorer health status than veterans without CWP. Five years after the conclusion of the first Gulf War (August 1990 to June 1991), we conducted a cross-sectional study of veterans who listed Iowa as the home of record using a stratified sampling design to determine their health status. We compared the prevalence of CWP between deployed and nondeployed veterans. Logistic and multiple linear regression models were constructed to test whether CWP was associated with comorbidities and health-related outcomes of interest. Five hundred ninety of 3695 veterans interviewed (16%) had CWP. Gulf deployment was associated with higher prevalence of CWP than deployment elsewhere (OR = 2.03, 95%CI = 1.60-2.58), after adjustment. Both deployed and nondeployed veterans with CWP reported more health care utilization and comorbidities and lower health-related quality of life scores than veterans without CWP. Deployed veterans were more likely to have CWP than nondeployed veterans, and CWP was associated with poor health outcomes. Military and medical personnel should be aware that efforts to prevent, identify, and treat CWP in veterans returning from the current war may be needed. PERSPECTIVE: This article indicates that deployed veterans may have an increased risk for development of CWP, which is associated with greater healthcare utilization and comorbidity and lower quality of life. The risk of poor health outcomes suggests that veterans returning from the present conflict should be screened for CWP on their return

Freedenfeld RN, Murray M, Fuchs PN, Kiser RS (2006) Decreased pain and improved quality of life in fibromyalgia patients treated with olanzapine, an atypical neuroleptic. Pain Pract 6:112-118.

Abstract: Fibromyalgia is a significant clinical problem associated with generalized pain and significant interference with daily activities. Although a variety of treatment modalities have been utilized, clinicians have struggled to find an effective means of treatment. Therefore, this study assessed the efficacy of the atypical neuroleptic olanzapine for the treatment of fibromyalgia symptoms. To examine the efficacy of olanzapine for the treatment of fibromyalgia symptoms, the charts of 51 patients treated with olanzapine were evaluated for improvements in pain and daily life functioning. At the time of initial assessment, patients had been diagnosed with a variety of medical and psychiatric disorders and a history of neuroleptic treatment. Pain was widespread and characteristic of pain associated with fibromyalgia. Pretreatment ratings on pain and the interference scales averaged 6.54-8.69 on a 0-10 scale. Post-treatment ratings on the same scales revealed significant improvement on virtually all scales. The benefits of olanzapine to improve fibromyalgia symptoms must, however, be carefully considered because there were a variety of side effects (i.e., weight gain, somnolence/sedation) that were of sufficient strength to cause a number of patients to discontinue treatment. In general, the data provide strong support that olanzapine can, in certain patients, improve symptoms associated with fibromyalgia in patients who have had limited success with other treatment modalities

Gamez W, Watson D, Doebbeling BN (2007) Abnormal personality and the mood and anxiety disorders: implications for structural models of anxiety and depression. J Anxiety Disord 21:526-539.

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

Genovese RF, Benton BJ, Oubre JL, Fleming PJ, Jakubowski EM, Mioduszewski RJ (2007) Determination of miosis threshold from whole-body vapor exposure to sarin in African green monkeys. Toxicology.

Abstract: We determined the threshold concentration of sarin vapor exposure producing miosis in African green monkeys (Chlorocebus aethiops). Monkeys (n=8) were exposed to a single concentration of sarin (0.069-0.701 mg/m^3) for 10min. Changes in pupil size were measured from photographs taken before and after the exposure. Sarin EC_{50} values for miosis were determined to be 0.166 mg/m^3 when miosis was defined as a 50% reduction in pupil area and 0.469 mg/m^3 when miosis was defined as a 50% reduction in pupil diameter. Monkeys were also evaluated for

behavioral changes from sarin exposure using a serial probe recognition test and performance remained essentially unchanged for all monkeys. None of the concentrations of sarin produced specific clinical signs of toxicity other than miosis. Sarin was regenerated from blood sampled following exposure in a concentration-dependent fashion. Consistent with a predominant inhibition of acetylcholinesterase (AChE), more sarin was consistently found in RBC fractions than in plasma fractions. Further, elimination of regenerated sarin from RBC fractions was slower than from plasma fractions. Blood samples following exposure also showed concentration-dependent inhibition of AChE activity and, to a lesser extent, butyrylcholinesterase activity. At the largest exposure concentration, AChE inhibition was substantial, reducing activity to approximately 40% of baseline. The results characterize sarin exposure concentrations that produce miosis in a large primate species in the absence of other overt signs of toxicity. Further, these results extend previous studies indicating that miosis is a valid early indicator for the detection of sarin vapor exposure

Genovese RF, Oubre JL, Jakubowski EM, Fleming PJ, Saxena A, Rockwood GA, Tipparaju P, Willmore CB (2007) 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 (5.87 µg/kg or 2.93 µg/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

Goldenberg DL (2007) Pharmacological treatment of fibromyalgia and other chronic musculoskeletal pain. Best Pract Res Clin Rheumatol 21:499-511.

Abstract: The pharmacologic management of fibromyalgia is based on the emerging evidence that pain in this disorder is primarily related to central pain sensitization. There is strong evidence that tricyclic antidepressants are effective, and moderate evidence for the effectiveness of serotonin reuptake inhibitors and dual serotonin-norepinephrine reuptake inhibitors. Recent work suggests that the anti-seizure medications pregabalin and gabepentin are also effective. The only analgesic demonstrated to be helpful is tramadol

Golier JA, Schmeidler J, Legge J, Yehuda R (2007) Twenty-four hour plasma cortisol and adrenocorticotropic hormone in Gulf War veterans: relationships to posttraumatic stress disorder and health symptoms. Biol Psychiatry 62:1175-1178.

Abstract: BACKGROUND: We aim to characterize the baseline functioning of the hypothalamic-pituitary-adrenal (HPA) axis in Gulf War veterans (GWV) and examine the extent to which posttraumatic stress disorder (PTSD) and unexplained health symptoms-which commonly co-occur-have similar or different biological correlates. METHODS: Thirty-one GWV, 20 with current PTSD and 11 without current or lifetime PTSD, and 16 healthy nondeployed subjects not exposed to the Gulf War theater underwent medical and psychiatric examination followed by blood sampling every half-hour over 24 hours for the measurement of cortisol and adrenocorticotropic hormone (ACTH). RESULTS: Gulf War veterans without PTSD or another psychiatric disorder had significantly lower 24-hour plasma ACTH levels, a significantly higher cortisol:ACTH ratio, and no difference in cortisol levels compared to nondeployed subjects and to GWV with PTSD, controlling for body mass index (BMI). Among GWV, health symptoms (mood and cognitive symptoms) were positively associated with, and hyperarousal symptoms were negatively associated with, the cortisol:ACTH ratio. Additionally, the self-reported acute effects of pesticides and of pyridostigmine bromide during deployment were associated with lower ACTH levels, controlling for BMI and PTSD. CONCLUSIONS: The data

provide evidence of HPA axis dysregulation in Gulf War veterans, which may be related to Gulf War deployment exposures. Despite the overlap of chronic unexplained health symptoms and PTSD in GWV, these symptom constellations appear to be biologically distinct

Guilmette RA, Durbin PW, Toohey RE, Bertelli L (2007) The NCRP Wound Model: Development and Application. Radiat Prot Dosimetry.
Abstract: The US National Council on Radiation Protection and Measurements, in collaboration with the International Commission on Radiological Protection, has been developing a biokinetic and dosimetric model for radionuclide-contaminated wounds. The finalised model is described briefly in this paper, together with the scientific basis and application. The multicompartment model uses first-order linear biokinetics to describe the retention and clearance of a radionuclide deposited in a wound site using seven default retention categories. Examples using plutonium nitrate in colloidal form and uranium in metal fragments show the behaviour of the less soluble forms of radionuclides in wounds, in which long-term retention is predicted. Using uranium as an example, the wound model is coupled to an International Commission on Radiological Protection systemic model to predict urinary excretion patterns for different physicochemical forms of uranium. The latter application is needed for bioassay interpretation

Guilmette RA, Parkhurst MA (2007) Dose Assessment for Inhalation Intakes in Complex, Energetic Environments: Experience from the US Capstone Study. Radiat Prot Dosimetry.
Abstract: Because of the lack of existing information needed to evaluate the risks from inhalation exposures to depleted uranium (DU) aerosols of US soldiers during the 1991 Persian Gulf War, the US Department of Defense funded an experimental study to measure the characteristics of DU aerosols created when Abrams tanks and Bradley fighting vehicles are struck with large-caliber DU penetrators, and a dose and risk assessment for individuals present in such vehicles. This paper describes some of the difficulties experienced in dose assessment modelling of the very complex DU aerosols created in the Capstone studies, e.g., high concentrations, heterogeneous aerosol properties, non-lognormal particle size distributions, triphasic in vitro dissolution and rapid time-varying functions of both DU air concentration and particle size. The approaches used to solve these problems along with example results are presented

Guo J (2007) Chronic fatigue syndrome treated by acupuncture and moxibustion in combination with psychological approaches in 310 cases. J Tradit Chin Med 27:92-95.
Abstract: OBJECTIVE: To observe clinical therapeutic effect of acupuncture and moxibustion (an oriental therapy utilizing mugwort herb) combined with a psychological approach on chronic fatigue syndrome (CFS). METHODS: The treatment was given by acupuncture plus moxibustion combined with a psychological approach based on differentiation of symptoms and signs in 310 cases. RESULTS: Of 310 cases observed, 275 cases (88.7%) were clinically cured, 28 cases (9%) improved, and 7 cases (2.3%) failed. CONCLUSION: Acupuncture plus moxibustion combined with a psychological approach is an effective therapy for CFS

Hancock S, Ehrich M, Hinckley J, Pung T, Jortner BS (2007) The effect of stress on the acute neurotoxicity of the organophosphate insecticide chlorpyrifos. Toxicol Appl Pharmacol 219:136-141.
Abstract: A study was conducted to determine if multiple exposures to several stress paradigms might affect the anticholinesterase effect of subsequently administered organophosphate insecticide chlorpyrifos. Male Sprague-Dawley rats were subject to daily periods of restraint, swimming, a combination of the two, or neither of the two (controls) (n=8/group) for 5 days per week over a six-week period. The most profound stress, as measured by reduced body weight gain and elevated levels of plasma corticosterone, was swimming. On day 39 of the study, shortly after the daily stress episode, one half of the rats in each group were dosed with 60 mg/kg chlorpyrifos subcutaneously. This had no effect on subsequent levels of plasma corticosterone. There were no stress-related differences in the degree of chlorpyrifos-induced inhibition of brain acetylcholinesterase in animals sacrificed on day 43

Hassett AL, Radvanski DC, Vaschillo EG, Vaschillo B, Sigal LH, Karavidas MK, Buyske S, Lehrer PM (2007) A pilot study of the efficacy of heart rate variability (HRV) biofeedback in patients with fibromyalgia. Appl Psychophysiol Biofeedback 32:1-10.
Abstract: Fibromyalgia (FM) is a non-inflammatory rheumatologic disorder characterized by musculoskeletal pain, fatigue, depression, cognitive dysfunction and sleep disturbance. Research suggests that autonomic dysfunction may account for some of the symptomatology of FM. An open label trial of biofeedback training was conducted to manipulate suboptimal heart rate variability (HRV), a key marker of autonomic dysfunction. METHODS: Twelve women ages 18-60 with FM completed 10 weekly sessions of HRV biofeedback. They were taught to breathe at their

resonant frequency (RF) and asked to practice twice daily. At sessions 1, 10 and 3-month follow-up, physiological and questionnaire data were collected. RESULTS: There were clinically significant decreases in depression and pain and improvement in functioning from Session 1 to a 3-month follow-up. For depression, the improvement occurred by Session 10. HRV and blood pressure variability (BPV) increased during biofeedback tasks. HRV increased from Sessions 1-10, while BPV decreased from Session 1 to the 3 month follow-up. CONCLUSIONS: These data suggest that HRV biofeedback may be a useful treatment for FM, perhaps mediated by autonomic changes. While HRV effects were immediate, blood pressure, baroreflex, and therapeutic effects were delayed. This is consistent with data on the relationship among stress, HPA axis activity, and brain function

Heaton KJ, Palumbo CL, Proctor SP, Killiany RJ, Yurgelun-Todd DA, White RF (2007) Quantitative magnetic resonance brain imaging in US army veterans of the 1991 Gulf War potentially exposed to sarin and cyclosarin. Neurotoxicology 28:761-769.
Abstract: BACKGROUND: In March 1991, a munitions storage complex at Khamisiyah, Iraq was destroyed, potentially exposing more than 100,000 US troops to low levels of the organophosphate nerve agents sarin and cyclosarin. Little is known about the neurophysiological effects of low-dose exposure to sarin/cyclosarin in humans, although some research has indicated subtle but persistent neurobehavioral and neurochemical changes in individuals exposed to sarin/cyclosarin at levels insufficient to produce obvious clinical symptoms. However, the neuroanatomy correlates of these changes are unclear. The current study examined the association between modeled estimates of sarin/cyclosarin exposure levels and volumetric measurements of gross neuroanatomy structures in 1991 Gulf War veterans with varying degrees of possible low-level sarin/cyclosarin exposure. METHODS: Twenty-six GW-deployed veterans recruited from the Devens Cohort Study participated. Magnetic resonance images of the brain were acquired and analyzed using morphometric techniques, producing volumetric measurements of white matter, gray matter, right and left lateral ventricles, and cerebrospinal fluid. Volumetric data were analyzed using exposure estimates obtained from refined models of the 1991 Khamisiyah presumed exposure hazard area. RESULTS: Binary comparisons of sarin/cyclosarin 'exposed' (N=13) and 'unexposed' (N=13) veterans revealed no differences in volumetric measurements of discrete brain tissues. However, linear trend analyses showed a significant association between higher levels of estimated sarin/cyclosarin exposure and both reduced white matter (adjusted parameter estimate=-4.64, $p<0.0001$) and increased right lateral ventricle (adjusted parameter estimate=.11, $p=0.0288$) and left lateral ventricle (adjusted parameter estimate=.13, $p<0.0001$) volumes. CONCLUSIONS: These findings suggest subtle but persistent central nervous system pathology in Gulf War veterans potentially exposed to low levels of sarin/cyclosarin and argue for further investigation of the long-term effects of low-dose sarin/cyclosarin exposures in humans

Helmer DA, Flanagan ME, Woolson RF, Doebbeling BN (2007) Health services use among Gulf War veterans and Gulf War era nondeployed veterans: a large population-based survey. Am J Public Health 97:2145-2148.
Abstract: We sought to analyze the self-reported hospitalization, emergency department visits, and outpatient visits of Persian Gulf War (deployed; n=1896) and Persian Gulf War-era (nondeployed; n=1799) military personnel 5 years post conflict to determine whether these groups had different rates of health care use. Compared with personnel who had not been deployed, personnel who had been deployed were more likely to have visited an emergency department (25% vs 21%; odds ratio [OR]=1.24; 95% confidence interval [CI] = 1.06, 1.51]). Among these groups, the National Guard and Reserve personnel were more likely to have been hospitalized than were the regular military personnel (OR= 1.65; 95% CI=1.21, 2.26)

Hodgson E, Rose RL (2007) The importance of cytochrome P450 2B6 in the human metabolism of environmental chemicals. Pharmacol Ther 113:420-428.
Abstract: Cytochrome P450 (CYP) 2B6 (CYP2B6) is a human CYP isoform found in variable amounts in the liver and other organs. It is known to be inducible and polymorphic and has a wide range of xenobiotic substrates. Studies of CYP2B6 to date have concentrated heavily on clinical drugs. In the present communication, however, we concentrate on its role in the metabolism of environmental xenobiotics. The term environment is used, in its broadest sense, to include natural ecosystems and agroecosystems as well as the industrial and indoor domestic environments. In essence, this excludes only clinical drugs and drugs of abuse. Many of these chemicals, including agrochemicals and industrial chemicals, can serve as substrates, inhibitors and/or inducers of CYP2B6, these activities being often modified by the existence of polymorphic variants. Metabolism-based interactions between environmental chemicals are discussed, as well as the emerging possibility of metabolic interactions between environmental chemicals and clinical drugs

Hoffman A, Eisenkraft A, Finkelstein A, Schein O, Rotman E, Dushnitsky T (2007) A decade after the Tokyo sarin attack: a review of neurological follow-up of the victims. Mil Med 172:607-610.
Abstract: OBJECTIVE: On March 20, 1995, sarin gas was used in Tokyo by members of the Japanese "Uhm-Shinrikiu" cult, killing 12 and injuring >5,500 innocent people. Most of the casualties were mildly injured. This article reviews the neurological follow-up data for some of the victims over the past decade. METHODS: We reviewed the published literature regarding neurological follow-up of the victims, dividing the data according to the time elapsed after the attack. RESULTS: The digit span test, finger-tapping test, and computerized posturography were the only performance tests that showed statistically significant differences between the victims and the control groups in some of the surveys. The main sequela 7 years after the attack was post-traumatic stress disorder. CONCLUSIONS: The results emphasize the need for a national preparedness program for such mass casualty events, led by national health systems. This should include long-term, neurological, follow-up monitoring with performance tests and a post-traumatic stress disorder screening test

Houpert P, Frelon S, Monleau M, Bussy C, Chazel V, Paquet F (2007) Heterogeneous Accumulation of Uranium in the Brain of Rats. Radiat Prot Dosimetry.
Abstract: Recent reports suggest that uranium can accumulate not only in known target organs, that is, kidneys or bones, but also in others such as central nervous system. In the present work, the accumulation of uranium in the brain of rats was studied after repeated exposure by inhalation, chronic exposure by ingestion and acute exposure by injection. For each route of administration, the amount of uranium entering the brain was low. The results showed different accumulation in the brain areas according to the route of intake. Injection gave a rather homogeneous distribution in the different brain areas, whereas both inhalation and ingestion yielded heterogeneous but specific accumulation. These differences in distribution suggest the operation of different mechanisms of delivery of uranium to the brain tissues

Ismail K, Kent K, Sherwood R, Hull L, Seed P, David AS, Wessely S (2007) Chronic fatigue syndrome and related disorders in UK veterans of the Gulf War 1990-1991: results from a two-phase cohort study. Psychol Med1-9.
Abstract: BACKGROUND: The aim was to determine the prevalence of chronic fatigue syndrome (CFS), chronic fatigue and fibromyalgia in UK military personnel after the Gulf War 1990-1991.MethodA two-phase cohort study was used. Three randomly selected subsamples identified from a population-based cross-sectional postal survey of over 10 000 current and ex-service UK military personnel (Gulf veterans were those deployed to the Gulf War 1990-1991; non-Gulf veterans were Bosnia peacekeepers 1992-1997 and those on active duty during the Gulf War 1990-1991 but not deployed) were recruited. Their disability status was assessed using the Short Form 36 physical functioning scale; Gulf veterans who reported physical disability (n=111) were compared with non-Gulf (n=133) veterans who reported similar levels of physical disability. Screening for known medical and psychiatric conditions was conducted to exclude medical explanations for disability and symptomatic distress. Standardised criteria for CFS, chronic fatigue and fibromyalgia were used. RESULTS: Disabled Gulf veterans were more likely to be overweight, have elevated gamma-glutamyl transferase levels and screen positive for hypertension. There were no other clinically significant differences in clinical markers for medically explainable conditions. Disabled Gulf veterans were more likely than similarly disabled Bosnia and Era veterans (adjusted odds ratio 7.8, 95% confidence interval 2.5-24.5) to meet the criteria for CFS. Rates for other medically unexplained conditions were not significantly increased. CONCLUSIONS: Symptoms in keeping with CFS account for a significant part of the symptomatic distress in Gulf veterans

Iversen A, Chalder T, Wessely S (2007) Gulf War Illness: lessons from medically unexplained symptoms. Clin Psychol Rev 27:842-854.
Abstract: Service in the Persian Gulf in 1991 is associated with increased reporting of symptoms and distress in a proportion of those who served there. Yet despite clear evidence of an increase in symptom burden and a decrease in well being, exhaustive clinical and laboratory based scientific research has failed to document many reproducible biomedical abnormalities in this group. Likewise, there has been no evidence of an increase in disease related mortality. Formal psychiatric disorders are twice as common in Gulf War veterans, as might be expected in the aftermath of any conflict, but this too is insufficient to explain the ill-health observed. Many service personnel who returned unwell believe that they have Gulf War Syndrome, and that their ill-health is due to exposures that they encountered in theatre. Research on multiple exposures to date has not generated a plausible aetiological mechanism for veterans' ill-health. Even if medical research has failed to provide a satisfactory explanation, it remains the case that many of those affected continue to be unwell and disabled some 15 years after returning from combat. For this reason, it is time that more attention is given to developing effective interventions to relieve their ill-health and distress. In this review we discuss the importance of the wider social context, individual illness beliefs and attributions and go on to outline a model of

continuing ill-health in Gulf veterans. The review concludes with some suggestions for future research priorities, in particular the need for further qualitative studies to further our understanding of the illness, in order that better treatments may be developed

Jaga K, Dharmani C (2007) The interrelation between organophosphate toxicity and the epidemiology of depression and suicide. Rev Environ Health 22:57-73.
Abstract: The literature on an association between organophosphate (OP) toxicity and depression or suicide is scarce. An interrelation exists among populations exposed to OPs, acute OP toxicity, neurobehavioral effects, depression, suicide, and fatality. Acute OP toxicity is characterized by the cholinergic syndrome with systemic and central nervous system effects. Organophosphate-induced neurobehavioral effects result in depression. A potential risk of depression and suicide exists in farm workers exposed to OPs. The sociodemographics of depression include age, gender, race, geographic region, social factors, economics, psychiatric disorders, medical conditions, and hereditary factors. Suicide is a major consequence of depression, with multiple sociodemographic risk factors. Developing countries have a higher incidence of OP toxicity, with limited information on the prevalence of depression. In these countries, the incidence of suicide is high, affecting more females. Suicide is more prevalent in rural areas, and in farming communities, commonly with ingestion of OPs. In industrialized countries, the incidence of OP toxicity is lower, but the prevalence of depression is higher. Suicide rates are lower in industrialized countries, affecting more males, the urban population, and farming communities. Other lethal methods of suicide, such as hanging, firearms, electrocution, and drug overdose are more common in industrialized countries. A potential risk of depression or suicide certainly exists from OP toxicity, largely depending on the epidemiology or sociodemographics of these disorders. Scientific evidence shows that the association between environmental toxicology and psychiatry has important public health implications

Jiang GC, Tidwell K, McLaughlin BA, Cai J, Gupta RC, Milatovic D, Nass R, Aschner M (2007) Neurotoxic potential of depleted uranium effects in primary cortical neuron cultures and in Caenorhabditis elegans. Toxicol Sci 99:553-565.
Abstract: Depleted uranium (DU) is an extremely dense metal that is used in radiation shielding, counterbalances, armor, and ammunition. In light of the public concerns about exposure to DU and its potential role in Gulf War Syndrome (GWS), this study evaluated the neurotoxic potential of DU using focused studies on primary rat cortical neurons and the nematode Caenorhabditis elegans. We examined cell viability, cellular energy metabolism, thiol metabolite oxidation, and lipid peroxidation following exposure of cultured neurons to DU, in the form of uranyl acetate. We concurrently evaluated the neurotoxicity of uranyl acetate in C. elegans using various neuronal-green fluourescent protein reporter strains to visualize neurodegeneration. Our studies indicate that uranyl acetate has low cytotoxic potential, and uranium exposure does not result in significant changes in cellular energy metabolism, thiol metabolite oxidation, or lipid peroxidation. Furthermore, our C. elegans studies do not show any significant neurodegeneration following uranyl acetate exposure. Together, these studies suggest that DU, in the form of uranyl acetate, has low neurotoxic potential. These findings should alleviate the some of public concerns regarding DU as an etiologic agent of neurodegenerative conditions associated with GWS

Jones AD, Miller BG, Walker S, Anderson J, Colvin AP, Hutchison PA, Soutar CA (2007) A normative value pilot study: levels of uranium in urine samples from UK civilians. Environ Res 104:216-223.
Abstract: A normative study of the levels of urinary uranium in the general UK population is needed for comparison with levels in UK military and ex-military personnel who served where munitions containing depleted uranium (DU) were used. As preparation, this pilot study trialled the process of collecting 24-h samples from adult male civilians, and compared the measurements from 24-h samples with those from spot samples taken over the subsequent 24h. The purpose was to assess the relative utility of the two types of samples. Twenty-five convalescent hospital in-patients were recruited as participants. Uranium concentrations in the 24-h samples ranged from 1 to 10.6 ng/l; in the spots, from not detectable to 38.1 ng/l. Normalised to creatinine, concentrations in the 24h samples ranged from approximately 100 to 800 ng/mol creatinine; in the spot samples, from not detectable to approximately 4000 ng/mol creatinine. The ranges appear similar to those reported for residents of the US. The distribution of spot sample results indicated that 95% of a participant's creatinine-adjusted concentrations from spot samples would be within the range 40-250% of his mean. Adjusting for creatinine almost entirely eliminated a slight indication of diurnal variation in urinary uranium concentration in spot samples. All the 24-h samples and 131 out of the 133 spot samples showed ratios of isotopes ^{238}U to ^{235}U consistent with natural uranium (i.e., neither enriched nor depleted). Slightly elevated ratios in two spot samples were not supported by other samples from the same participants, indicating that slightly elevated ratios may be recorded on very low concentration (<1 ng/l samples. In the main, quantification of this isotope ratio from spot samples was only slightly more variable than from 24-h samples. Complete 24-h urine samples gave better precision

than spot samples in estimating uranium concentrations at these low levels, but presented more logistic difficulties in the collection of the samples. Clarification of the relative merits of alternative sampling strategies enables the design of a wider study to be optimised

Jones KD, Deodhar P, Lorentzen A, Bennett RM, Deodhar AA (2007) Growth hormone perturbations in fibromyalgia: a review. Semin Arthritis Rheum 36:357-379.
Abstract: OBJECTIVE: Fibromyalgia (FM) is a syndrome characterized by chronic widespread pain, fatigue, disrupted sleep, depression, and physical deconditioning. In this article, we review the literature on the normal activity of the hypothalamic-pituitary-growth hormone-insulin-like growth factor-1 (HP-GH-IGF-1) axis and its perturbations in FM subjects. METHODS: Studies included in this review were accessed through an English language search of Cochrane Collaboration Reviews. Keyword MeSH terms included "fibromyalgia," "growth hormone" (GH), or "insulin-like growth factor-1" (IGF-1). RESULTS: Twenty-six studies enrolling 2006 subjects were reviewed. Overall, low levels of IGF-1 were found in a subgroup of subjects. Growth hormone stimulation tests often revealed a suboptimal response, which did not always correlate with IGF-1 levels. No consistent defects in pituitary function were found. Of the 3 randomized placebo controlled studies, only 9 months of daily injectable recombinant GH reduced FM symptoms and normalized IGF-1. CONCLUSIONS: These studies suggest that pituitary function is normal in FM and that reported changes in the HP-GH-IGF-1 axis are most likely hypothalamic in origin. The therapeutic efficacy of supplemental GH therapy in FM requires further study before any solid recommendations can be made

Katafuchi T, Kondo T, Take S, Yoshimura M (2006) Brain cytokines and the 5-HT system during poly I:C-induced fatigue. Ann N Y Acad Sci 1088:230-237.
Abstract: Fatigue is evoked not only by peripheral factors, such as muscle fatigue, but also by the central nervous system (CNS). For example, it is generally known that the feeling of fatigue is greatly influenced by psychological aspects, such as motivation. However, little is known about the central mechanisms of fatigue. The clinical symptoms of chronic fatigue syndrome (CFS) are shown to include disorders in neuroendocrine, autonomic, and immune systems. On the other hand, it has been demonstrated that cytokines produced in the brain play significant roles in neural-immune interactions through their various central actions, including hypothalamo-pituitary and sympathetic activation, as well as immunosuppression. In this article, using the immunologically induced fatigue model, which was achieved by intraperitoneal (i.p.) injection of synthetic double-stranded RNAs, polyriboinosinic: polyribocytidylic acid (poly I:C) in rats, we show an involvement of brain interferon-α (IFN-α) and serotonin (5-HT) transporter (5-HTT) in the central mechanisms of fatigue. In the poly I:C-induced fatigue rats, expression of IFN-α and 5-HTT increased, while extracellular concentration of 5-HT in the medial prefrontal cortex decreased, probably on account of the enhanced expression of 5-HTT. Since the poly I:C-induced reduction of the running wheel activity was attenuated by a 5-HT(1A) receptor agonist, but not by 5-HT(2), 5-HT(3), or dopamine D(3) receptor agonists, it is suggested that the decrease in 5-HT actions on 5-HT(1A) receptors may at least partly contribute to the poly I:C-induced fatigue

Kelsall HL, Sim MR, Ikin JF, Forbes AB, McKenzie DP, Glass DC, Ittak P (2007) Reproductive health of male Australian veterans of the 1991 Gulf War. BMC Public Health 7:79.
Abstract: BACKGROUND: Since the 1991 Gulf War concerns have been raised about the effects of deployment to the Gulf War on veterans' health. Studies of the reproductive health of Gulf War veterans have reported varied findings. METHODS: We undertook a cross-sectional study of male Australian Gulf War veterans (n = 1,424) and a randomly sampled military comparison group (n = 1,548). The study was conducted from August 2000 to April 2002. A postal questionnaire included questions about difficulties achieving pregnancy, pregnancy outcomes including live births, stillbirths, miscarriages and terminations; and for all live births gestation, birth weight, sex, and any cancers, birth defects, chromosomal abnormalities or serious health problems. RESULTS: Male Gulf War veterans reported slightly increased risk of fertility difficulties following the Gulf War (odds ratio [OR] 1.4; 95% confidence interval [CI] 1.0-1.8), but were more successful at subsequently fathering a child (OR 1.8; 95% CI 1.3-2.6). The study groups reported similar rates of pregnancies and live births. There was no increased risk in veterans of miscarriage, stillbirth, or terminations. Children of male Gulf War veterans born after the period of the Gulf War were not at greater risk of being born prematurely, having a low birth weight, or having a birth defect or chromosomal abnormality (OR 1.0; 95% CI 0.6-1.6). The numbers of cancers and deaths in children were too small to draw any firm conclusions. CONCLUSION: The results of this study do not show an increased risk of adverse reproductive outcome in Australian male Gulf War veterans

Kim SH (2007) Skin biopsy findings: implications for the pathophysiology of fibromyalgia. Med Hypotheses 69:141-144.
Abstract: The mechanisms responsible for symptom expression in fibromyalgia (FM) are complex. The most consistently detected objective abnormalities in FM involve pain-processing systems. Up to recently, central nervous system was a primary focus of investigations in FM. Although it is unlikely that FM occurs because of primary disorders of the peripheral tissues, there are still data to suggest that some abnormalities can be detected in the periphery. With the recognition of abnormalities in skin of some FM patients, it is now apparent that the role of peripheral nerve endings in FM is much greater than previously thought. The aim of this paper is to review literature concerning the skin biopsy findings of FM patients and discuss their potential relevance to FM. This paper suggests that patients with FM represent a state of the dysfunction of descending, antinociceptive pathways and low hypothalamic-pituitary-adrenal function. This state is further proposed to result in many skin biopsy findings associated with the disorder, including increased N-methyl-d-aspartate receptors subtype 2D expression, neurogenic inflammation and characteristic electron microscopic findings. Future direction of research would be identification of specific laboratory markers such as skin biopsy for diagnostic and clinical evaluation purposes in FM

Knoop H, Prins JB, Stulemeijer M, van der Meer JW, Bleijenberg G (2007) The effect of cognitive behaviour therapy for chronic fatigue syndrome on self-reported cognitive impairments and neuropsychological test performance. J Neurol Neurosurg Psychiatry 78:434-436.
Abstract: BACKGROUND: Patients with chronic fatigue syndrome (CFS) often have concentration and memory problems. Neuropsychological test performance is impaired in at least a subgroup of patients with CFS. Cognitive behavioural therapy (CBT) for CFS leads to a reduction in fatigue and disabilities. AIM: To test the hypothesis that CBT results in a reduction of self-reported cognitive impairment and in an improved neuropsychological test performance. METHODS: Data of two previous randomised controlled trials were used. One study compared CBT for adult patients with CFS, with two control conditions. The second study compared CBT for adolescent patients with a waiting list condition. Self-reported cognitive impairment was assessed with questionnaires. Information speed was measured with simple and choice reaction time tasks. Adults also completed the symbol digit-modalities task, a measure of complex attentional function. RESULTS: In both studies, the level of self-reported cognitive impairment decreased significantly more after CBT than in the control conditions. Neuropsychological test performance did not improve. CONCLUSIONS: CBT leads to a reduction in self-reported cognitive impairment, but not to improved neuropsychological test performance. The findings of this study support the idea that the distorted perception of cognitive processes is more central to CFS than actual cognitive performance

Knoop H, Stulemeijer M, Prins JB, van der Meer JW, Bleijenberg G (2007) Is cognitive behaviour therapy for chronic fatigue syndrome also effective for pain symptoms? Behav Res Ther 45:2034-2043.
Abstract: Patients with chronic fatigue syndrome (CFS) frequently report chronic pain symptoms. Cognitive behavioural therapy (CBT) for CFS results in a reduction of fatigue, but is not aimed at pain symptoms. In this study, we tested the hypothesis that a successful treatment of CFS can also lead to a reduction of pain. The second objective was to explore possible mechanisms of changes in pain. The third objective was to assess the predictive value of pain for treatment outcome. Data from two previous CBT studies were used, one of adult CFS patients (n=96) and one of adolescent CFS patients (n=32). Pain severity was assessed with a daily self-observation list at baseline and post-treatment. The location of pain in adults was assessed with the McGill Pain Questionnaire (MPQ). Patients were divided into recovered and non-recovered groups. Recovery was defined as reaching a post-treatment level of fatigue within normal range. Recovered adult and adolescent CFS patients reported a significant reduction of pain severity compared to non-recovered patients. Recovered adult patients also had fewer pain locations following treatment. The decrease in fatigue predicted the change in pain severity. In adult patients, a higher pain severity at baseline was associated with a negative treatment outcome

Komaroff AL (2006) Is human herpesvirus-6 a trigger for chronic fatigue syndrome? J Clin Virol 37 Suppl 1:S39-S46.
Abstract: Chronic fatigue syndrome (CFS) is an illness currently defined entirely by a combination of non-specific symptoms. Despite this subjective definition, CFS is associated with objective underlying biological abnormalities, particularly involving the nervous system and immune system. Most studies have found that active infection with human herpesvirus-6 (HHV-6)--a neurotropic, gliotropic and immunotropic virus--is present more often in patients with CFS than in healthy control and disease comparison subjects, yet it is not found in all patients at the time of testing. Moreover, HHV-6 has been associated with many of the neurological and immunological findings in patients with CFS.

Finally, CFS, multiple sclerosis and seizure disorders share some clinical and laboratory features and, like CFS, the latter two disorders also are being associated increasingly with active HHV-6 infection. Therefore, it is plausible that active infection with HHV-6 may trigger and perpetuate CFS in a subset of patients

Kuchinad A, Schweinhardt P, Seminowicz DA, Wood PB, Chizh BA, Bushnell MC (2007) Accelerated brain gray matter loss in fibromyalgia patients: premature aging of the brain? J Neurosci 27:4004-4007.
Abstract: Fibromyalgia is an intractable widespread pain disorder that is most frequently diagnosed in women. It has traditionally been classified as either a musculoskeletal disease or a psychological disorder. Accumulating evidence now suggests that fibromyalgia may be associated with CNS dysfunction. In this study, we investigate anatomical changes in the brain associated with fibromyalgia. Using voxel-based morphometric analysis of magnetic resonance brain images, we examined the brains of 10 female fibromyalgia patients and 10 healthy controls. We found that fibromyalgia patients had significantly less total gray matter volume and showed a 3.3 times greater age-associated decrease in gray matter than healthy controls. The longer the individuals had had fibromyalgia, the greater the gray matter loss, with each year of fibromyalgia being equivalent to 9.5 times the loss in normal aging. In addition, fibromyalgia patients demonstrated significantly less gray matter density than healthy controls in several brain regions, including the cingulate, insular and medial frontal cortices, and parahippocampal gyri. The neuroanatomical changes that we see in fibromyalgia patients contribute additional evidence of CNS involvement in fibromyalgia. In particular, fibromyalgia appears to be associated with an acceleration of age-related changes in the very substance of the brain. Moreover, the regions in which we demonstrate objective changes may be functionally linked to core features of the disorder including affective disturbances and chronic widespread pain

LaDou J (2007) "Gulf war syndrome" may be related to circadian dysrhythmia. Int J Occup Environ Health 13:125-127.
Abstract: An Institute of Medicine (IOM) review found that the data obtained from research addressing the health issues of Gulf War veterans do not satisfactorily clarify the origins, extent, and long-term implications of their health problems. The IOM committee concluded that there should have been more screening and medical examinations of deployed personnel before and after service in the Gulf. The many possible causes of the "Gulf War syndrome" examined, however, did not include circadian dysrhythmia or desynchronosis. It would have been possible to determine the level of desynchronosis in the returning Gulf War veterans, and to follow them into their subsequent pursuits to determine whether chronic desynchronosis was present in those who had persistent symptoms. If circadian dysrhythmia is found to be present in veterans now returning from the Gulf, they should receive treatment to correct the problem before they develop chronic desynchronosis

Laske C, Stransky E, Eschweiler GW, Klein R, Wittorf A, Leyhe T, Richartz E, Kohler N, Bartels M, Buchkremer G, Schott K (2007) Increased BDNF serum concentration in fibromyalgia with or without depression or antidepressants. J Psychiatr Res 41:600-605.
Abstract: Fibromyalgia (FM) is still often viewed as a psychosomatic disorder. However, the increased pain sensitivity to stimuli in FM patients is not an "imagined" histrionic phenomena. Pain, which is consistently felt in the musculature, is related to specific abnormalities in the CNS pain matrix. Brain-derived neurotrophic factor (BDNF) is an endogenous protein involved in neuronal survival and synaptic plasticity of the central and peripheral nervous system (CNS and PNS). Several lines of evidence converged to indicate that BDNF also participates in structural and functional plasticity of nociceptive pathways in the CNS and within the dorsal root ganglia and spinal cord. In the latter, release of BDNF appears to modulate or even mediate nociceptive sensory inputs and pain hypersensitivity. We were interested, if BDNF serum concentration may be altered in FM. The present pilot study assessed to our knowledge for the first time BDNF serum concentrations in 41 FM patients in comparison to 45 age-matched healthy controls. Mean serum levels of BDNF in FM patients (19.6 ng/ml; SD 3.1) were significantly increased as compared to healthy controls (16.8 ng/ml; SD 2.7; $p<0.0001$). In addition, BDNF serum concentrations in FM patients were independent from age, gender, illness duration, preexisting recurrent major depression and antidepressive medication in low doses. In conclusion, the results from our study indicate that BDNF may be involved in the pathophysiology of pain in FM. Nevertheless, how BDNF increases susceptibility to pain is still not known

Lawlor DA, Day IN, Gaunt TR, Hinks LJ, Timpson N, Ebrahim S, Davey SG (2007) The association of the paraoxonase (PON1) Q192R polymorphism with depression in older women: findings from the British Women's Heart and Health Study. J Epidemiol Community Health 61:85-87.
Abstract: BACKGROUND: The association between the R allele of PON1 Q192R and symptoms reported by sheep dippers and Gulf War veterans has been used to suggest a biological basis for these symptoms. In the absence of such studies in non-occupational populations, these conclusions may not be valid. OBJECTIVE: To examine the association of paraoxonase (PON1) Q192R with a report of ever being diagnosed with depression among a random sample of 3266 British women, aged 60-79 years. RESULTS: The R allele of PON1 Q192R was associated with depression: per-allele odds ratio 1.22 (95% confidence interval: 1.05 to 1.41) in this population. CONCLUSIONS: These findings suggest that the association of PON1 Q192R with symptoms of depression in occupationally exposed groups may be driven by exposure to toxins that everyone in the general population is exposed to rather than exposure to toxins specifically used by sheep dippers or Gulf War veterans, or that other mechanisms underlie the association. This is because the study population in which we have found an association consisted of British women aged 60-79 years, few of whom were sheep dippers or Gulf War veterans. When using genotype-outcome associations to infer causality with respect to an environmental exposure modified by the genotype, it is important to examine these associations in general populations and in those specifically exposed to the putative agent. The possible role of PON1 Q192R in psychiatric morbidity requires further examination

Lee WJ, Alavanja MC, Hoppin JA, Rusiecki JA, Kamel F, Blair A, Sandler DP (2007) Mortality among pesticide applicators exposed to chlorpyrifos in the Agricultural Health Study. Environ Health Perspect 115:528-534.
Abstract: BACKGROUND: Chlorpyrifos is one of the most widely used organophosphate insecticides in the United States. Although the toxicity of chlorpyrifos has been extensively studied in animals, the epidemiologic data are limited. OBJECTIVE: To evaluate whether agricultural chlorpyrifos exposure was associated with mortality, we examined deaths among pesticide applicators in the Agricultural Health Study, a prospective study of licensed pesticide applicators in Iowa and North Carolina. METHODS: A total of 55,071 pesticide applicators were included in this analysis. Detailed pesticide exposure data and other information were obtained from self-administered questionnaires completed at the time of enrollment (1993-1997). Lifetime chlorpyrifos use was divided into tertiles. Poisson regression analysis was used to evaluate the exposure-response relationships between chlorpyrifos use and causes of death after adjustment for potential confounders. RESULTS: A total of 1,851 deaths (588 among chlorpyrifos users) were observed during the study period, 1993-2001. The relative risk (RR) of death from all causes combined among applicators exposed to chlorpyrifos was slightly lower than that for nonexposed applicators (RR = 0.90; 95% confidence interval, 0.81-1.01). For most causes of death analyzed, there was no evidence of an exposure-response relationship. However, the relative risks for mortality from suicide and non-motor-vehicle accidents were increased 2-fold in the highest category of chlorpyrifos exposure days. CONCLUSIONS: Our findings of a possible association between chlorpyrifos use and external causes of death were based on small numbers. However, the findings may reflect a link between chlorpyrifos and depression or other neurobehavioral symptoms that deserves further evaluation

Levine PH, Richardson PK, Zolfaghari L, Cleary SD, Geist CE, Potolicchio S, Young HA, Simmens SJ, Schessel D, Williams K, Mahan CM, Kang HK (2006) A study of Gulf War veterans with a possible deployment-related syndrome. Arch Environ Occup Health 61:271-278.
Abstract: A previous symptom-based survey of veterans of the 1990-1991 Persian Gulf War suggested a neurological syndrome (blurred vision, loss of balance/dizziness, tremors/shaking, and speech difficulty). The authors conducted the present study to determine whether specific findings could indicate an organic basis for this possible syndrome. They completed an extensive clinical and laboratory evaluation on Gulf War veterans with all 4 symptoms, using 3 comparison groups. A single clinically based neurological syndrome could not be identified. No deployment-related exposure appeared to explain the pattern of symptoms, but this evaluation suggested comorbidities and possibly multiple vaccines as important contributors. Many of the neurological symptoms reported by the studied veterans appear to have an organic basis, but comorbidities must be excluded before researchers can conclude that a definitive syndrome exists

Linares V, Sanchez DJ, Belles M, Albina L, Gomez M, Domingo JL (2007) Pro-oxidant effects in the brain of rats concurrently exposed to uranium and stress. Toxicology 236:82-91.
Abstract: Metal toxicity may be associated with increased rates of reactive oxygen species (ROS) generation within the central nervous system (CNS). Although the kidney is the main target organ for uranium (U) toxicity, this metal can also accumulate in brain. In this study, we investigated the modifications on endogenous antioxidant capacity and oxidative damage in several areas of the brain of U-exposed rats. Eight groups of adult male rats received uranyl

acetate dihydrate (UAD) in the drinking water at 0, 10, 20, and 40 mg/kg/day for 3 months. Animals in four groups were concurrently subjected to restraint stress during 2h/day throughout the study. At the end of the experimental period, cortex, hippocampus and cerebellum were removed and processed to examine the following stress markers: reduced glutathione (GSH), oxidized glutathione (GSSG), glutathione reductase (GR), glutathione peroxidase (GPx), superoxide dismutase (SOD), catalase (CAT), thiobarbituric acid reactive substances (TBARS), as well as U concentrations. The results show that U significantly accumulated in hippocampus, cerebellum and cortex after 3 months of exposure. Moreover, UAD exposure promoted oxidative stress in these cerebral tissues. In cortex and cerebellum, TBARS levels were positively correlated with the U content, while in cerebellum GSSG and GSH levels were positively and negatively correlated, respectively, with U concentrations. In hippocampus, CAT and SOD activities were positively correlated with U concentration. The present results suggest that chronic oral exposure to UAD can cause progressive perturbations on physiological brain levels of oxidative stress markers. Although at the current UAD doses restraint scarcely showed additional adverse effects, its potential influence should not be underrated

Lucas KE, Rowe PC, Armenian HK (2007) Latency and exposure-health associations in Gulf War veterans with early fatigue onsets: a case-control study. Ann Epidemiol 17:799-806.
Abstract: PURPOSE: To see if self-reported exposures were associated with health in early-onset Gulf War illnesses (GWIs) cases and healthy Gulf War veteran controls. METHODS: Forty-nine cases and 44 controls completed questionnaires about wartime exposures and symptoms experienced. Odds ratios were calculated using 2 x 2 tables and logistic regression. The incubation curve of fatigue onsets in cases was drawn to highlight exposure/health associations using Sartwell's method and tested with the Shapiro-Wilk test. The incubation period was defined as the time from arrival in the Persian Gulf to fatigue onset. RESULTS: The incubation curve was right skewed and log normally distributed ($p = 0.48$; $p > 0.05$ indicates log normality), suggesting an association between a wartime exposure and fatigue. Exposure to oil fire smoke, pesticides, contaminated food or water, dead animals, scud missile attacks, dead bodies, prisoners of war, artillery or small arms fire, and chemical suits was significantly associated with GWIs. Pyridostigmine bromide (PB) was the only continuous exposure significantly associated with GWIs. The odds of having GWIs increased by 1.3% for every PB pill taken (95% confidence interval 1.001-1.02). There were significant trends toward worse health with greater intake of PB. CONCLUSIONS: These analyses suggest that wartime exposures, including exposure to PB, are associated with fatigue

Mach M, Grubbs RD, Price WA, Nagaoka M, Dubovicky M, Lucot JB (2007) Delayed behavioral and endocrine effects of sarin and stress exposure in mice. J Appl Toxicol.
Abstract: The organophosphorus agent sarin is a potent inhibitor of acetylcholinesterase. Experiments tested the influence of exposure to low doses of sarin along with psychological stress on delayed behavioral and endocrine changes in mice. Motor activity, acoustic startle response (ASR), pre-pulse inhibition (PPI) of ASR, activity of cholinesterase in blood and catecholamine levels in adrenals were evaluated after low dose sarin exposure (3 x 0.4 LD(50) subcutaneously) combined with chronic intermittent stress in C57BL/6J mice. While sarin alone produced depression of motor activity, no interaction of the stress with sarin exposure was observed. Cholinesterase activity was significantly reduced 24 h after exposure to sarin; however, the basal activity was re-established 3 weeks later. The combination of low dose sarin exposure and stress produced delayed behavioral change manifested as excessive grooming together with endocrine alterations in adrenals 7 weeks after exposure. The size of the adrenals in the combined exposure group was increased and the concentration of catecholamines was significantly decreased. In conclusion, these findings indicate that sarin in low doses is more dangerous when combined with shaker stress inducing delayed behavioral and endocrine changes. Copyright (c) 2007 John Wiley & Sons, Ltd

Maes M, Mihaylova I, Bosmans E (2007) Not in the mind of neurasthenic lazybones but in the cell nucleus: patients with chronic fatigue syndrome have increased production of nuclear factor kappa β. Neuro Endocrinol Lett 28:456-462.
Abstract: There is now some evidence that chronic fatigue syndrome is accompanied by an activation of the inflammatory response system and by increased oxidative and nitrosative stress. Nuclear factor kappa beta (NF-κ-β) is the major upstream, intracellular mechanism which regulates inflammatory and oxidative stress mediators. In order to examine the role of NF-κ-β in the pathophysiology of CFS, this study examines the production of NF-κ-β p50 in unstimulated, 10 ng/mL TNF-α (tumor necrosis factor alpha) and 50 ng/mL PMA (phorbolmyristate acetate) stimulated peripheral blood lymphocytes of 18 unmedicated patients with CFS and 18 age-sex matched controls. The unstimulated ($F=19.4$, $df=1/34$, $p=0.0002$), TNF-α ($F=14.0$, $df=1/34$, $p=0.0009$) and PMA-($F=7.9$, $df=1/34$, $p=0.008$) stimulated production of NF-κ-β were significantly higher in CFS patients than in controls. There were significant and positive

correlations between the production of NF-κ-β and the severity of illness as measured with the FibroFatigue scale and with symptoms, such as aches and pain, muscular tension, fatigue, irritability, sadness, and the subjective feeling of infection. The results show that an intracellular inflammatory response in the white blood cells plays an important role in the pathophysiology of CFS and that previous findings on increased oxidative stress and inflammation in CFS may be attributed to an increased production of NF-κ-β. The results suggest that the symptoms of CFS, such as fatigue, muscular tension, depressive symptoms and the feeling of infection reflect a genuine inflammatory response in those patients. It is suggested that CFS patients should be treated with antioxidants, which inhibit the production of NF-κ-β, such as curcumin, N-Acetyl-Cysteine, quercitin, silimarin, lipoic acid and omega-3 fatty acids

Maes M, Mihaylova I, Kubera M, Bosmans E (2007) Not in the mind but in the cell: increased production of cyclo-oxygenase-2 and inducible NO synthase in chronic fatigue syndrome. Neuro Endocrinol Lett 28:463-469.
Abstract: Chronic fatigue syndrome (CFS) is a medically unexplained disorder, characterized by profound fatigue, infectious, rheumatological and neuropsychiatric symptoms. There is, however, some evidence that CFS is accompanied by signs of increased oxidative stress and inflammation in the peripheral blood. This paper examines the role of the inducible enzymes cyclo-oxygenase (COX-2) and inducible NO synthase (iNOS) in the pathophysiology of CFS. Toward this end we examined the production of COX-2 and iNOS by peripheral blood lymphocytes (PBMC) in 18 CFS patients and 18 normal volunteers and examined the relationships between those inflammatory markers and the severity of illness as measured by means of the FibroFatigue scale and the production of the transcription factor nuclear factor kappa beta (NF-κ-β). We found that the production of COX-2 and iNOS was significantly higher in CFS patients than in normal controls. There were significant and positive intercorrelations between COX-2, iNOS and NF-κ-β and between COX-2 and iNOS, on the one hand, and the severity of illness, on the other. The production of COX-2 and iNOS by PBMCs was significantly related to aches and pain, muscular tension, fatigue, concentration difficulties, failing memory, sadness and a subjective experience of infection. The results suggest that a) an intracellular inflammatory response in the white blood cells plays an important role in the pathophysiology of CFS; b) the inflammatory response in CFS is driven by the transcription factor NF-κ-β; c) symptoms, such as fatigue, pain, cognitive defects and the subjective feeling of infection, indicates the presence of a genuine inflammatory response in CFS patients; and d) CFS patients may be treated with substances that inhibit the production of COX-2 and iNOS

Maquet D, Demoulin C, Croisier JL, Crielaard JM (2007) Benefits of physical training in fibromyalgia and related syndromes. Ann Readapt Med Phys 50:363-62.
Abstract: OBJECTIVE: To review the published information on physical training for fibromyalgia (FM) and related syndromes. METHODS: A search of Medline literature (via Ovid and PubMed) with the following keywords: FM, chronic fatigue syndrome, therapy, rehabilitation, aerobic, exercise, and cognitive behavioral therapy. The reference lists of articles were examined for additional related articles. RESULTS: Several studies investigated the benefits of graded exercise therapy for patients with FM or related syndromes. Although some systematic reviews have not established an unequivocal benefit of physical training, most authors report a benefit for patients with chronic pain or fatigue. Ideally, such a therapy should be a part of multidisciplinary program. Muscular rehabilitation is reserved for preventing the deconditioning syndrome often reported in patients and the vicious cycle of pain, avoidance and inactivity behaviors, or even kinesiophobia, deconditioning, incapacity and psychological distress. CONCLUSION: This review emphasizes the relevance of graded physical training for treating FM and related syndromes. The development of rehabilitation centers, with experts able to propose a relevant therapy to patients with chronic pain or fatigue, should help alleviate this public health problem

Mayhew E, Ernst E (2007) Acupuncture for fibromyalgia--a systematic review of randomized clinical trials. Rheumatology (Oxford) 46:801-804.
Abstract: OBJECTIVE: Acupuncture is often used and frequently advocated for the symptomatic treatment of fibromyalgia. A systematic review has previously demonstrated encouraging findings. As it is now outdated, we wanted to update it. METHODS: We searched seven electronic databases for relevant randomized clinical trials (RCTs). The data were extracted and validated independently by both authors. As no meta-analysis seemed possible, the results were evaluated in narrative form. RESULTS: Five RCTs met our inclusion criteria, all of which used acupuncture as an adjunct to conventional treatments. Their methodological quality was mixed and frequently low. Three RCTs suggested positive but mostly short-lived effects and two yielded negative results. There was no significant difference between the quality of the negative and the positive RCTs. All positive RCTs used electro-

acupuncture. CONCLUSION: The notion that acupuncture is an effective symptomatic treatment for fibromyalgia is not supported by the results from rigorous clinical trials. On the basis of this evidence, acupuncture cannot be recommended for fibromyalgia

McBeth J, Silman AJ, Gupta A, Chiu YH, Ray D, Morriss R, Dickens C, King Y, Macfarlane GJ (2007) Moderation of psychosocial risk factors through dysfunction of the hypothalamic-pituitary-adrenal stress axis in the onset of chronic widespread musculoskeletal pain: findings of a population-based prospective cohort study. Arthritis Rheum 56:360-371.
Abstract: OBJECTIVE: To test the hypothesis that abnormalities in the hypothalamic-pituitary-adrenal (HPA) stress-response system would act as an effect moderator between HPA function and the onset of chronic widespread pain (CWP). METHODS: We conducted a population-based prospective cohort study. Current pain and psychosocial status were ascertained in 11,000 subjects. Of the 768 eligible subjects free of CWP but at future risk based on their psychosocial profile, 463 were randomly selected, and 267 (57.7%) consented to assessment of their HPA axis function. Diurnal function was measured by assessing levels of salivary cortisol in the morning (9:00 AM) and evening (10:00 PM). Serum cortisol levels were measured after an overnight low-dose (0.25 mg) dexamethasone suppression test and a potentially stressful clinical examination. All subjects were followed up 15 months later to identify cases of new-onset CWP. RESULTS: A total of 241 subjects (94.9%) completed the followup study, and 28 (11.6%) reported the new onset of CWP. High levels of cortisol post-dexamethasone (odds ratio [OR] 3.53, 95% confidence interval [95% CI] 1.17-10.65), low levels in morning saliva (OR 1.43, 95% CI 0.52-3.94), and high levels in evening saliva (OR 2.32, 95% CI 0.64-8.42) were all associated with CWP. These 3 factors were found to be independent and additive predictors of CWP (OR for all 3 factors 8.5, 95% CI 1.5-47.9) in analyses controlling for age, sex, depression, sleep disturbance, recent traumatic life events, and pain status. One or more of these 3 HPA factors identified 26 (92.9%) cases of new-onset CWP. CONCLUSION: Among a group of psychologically at-risk subjects, dysfunction of the HPA axis helps to distinguish those who will and will not develop new-onset CWP

McDiarmid MA, Engelhardt SM, Oliver M, Gucer P, Wilson PD, Kane R, Cernich A, Kaup B, Anderson L, Hoover D, Brown L, Albertini R, Gudi R, Jacobson-Kram D, Squibb KS (2007) Health surveillance of Gulf War I veterans exposed to depleted uranium: updating the cohort. Health Phys 93:60-73.
Abstract: A cohort of seventy-four 1991 Gulf War soldiers with known exposure to depleted uranium (DU) resulting from their involvement in friendly-fire incidents with DU munitions is being followed by the Baltimore Veterans Affairs Medical Center. Biennial medical surveillance visits designed to identify uranium-related changes in health have been conducted since 1993. On-going systemic exposure to DU in veterans with embedded metal fragments is indicated by elevated urine uranium (U) excretion at concentrations up to 1,000-fold higher than that seen in the normal population. Health outcome results from the subcohort of this group of veterans attending the 2005 surveillance visit were examined based on two measures of U exposure. As in previous years, current U exposure is measured by determining urine U concentration at the time of their surveillance visit. A cumulative measure of U exposure was also calculated based on each veteran's past urine U concentrations since first exposure in 1991. Using either exposure metric, results continued to show no evidence of clinically significant DU-related health effects. Urine concentrations of retinol binding protein (RBP), a biomarker of renal proximal tubule function, were not significantly different between the low vs. high U groups based on either the current or cumulative exposure metric. Continued evidence of a weak genotoxic effect from the on-going DU exposure as measured at the HPRT (hypoxanthine-guanine phosphoribosyl transferase) locus and suggested by the fluorescent in-situ hybridization (FISH) results in peripheral blood recommends the need for continued surveillance of this population

McLean SA, Williams DA, Stein PK, Harris RE, Lyden AK, Whalen G, Park KM, Liberzon I, Sen A, Gracely RH, Baraniuk JN, Clauw DJ (2006) Cerebrospinal fluid corticotropin-releasing factor concentration is associated with pain but not fatigue symptoms in patients with fibromyalgia. Neuropsychopharmacology 31:2776-2782.
Abstract: Previous studies have identified stress system dysregulation in fibromyalgia (FM) patients; such dysregulation may be involved in the generation and/or maintenance of pain and other symptoms. Corticotropin-releasing factor (CRF) is the principal known central nervous system mediator of the stress response; however, to date no studies have examined cerebrospinal fluid (CSF) CRF levels in patients with FM. The relationship between CSF CRF level, heart rate variability (HRV), and pain, fatigue, and depressive symptoms was examined in patients with FM. Among participants (n=26), CSF CRF levels were associated with sensory pain symptoms (r=0.574, p=0.003) and affective pain symptoms (r=0.497, p=0.011), but not fatigue symptoms. Increased HRV was also strongly associated with increased CSF CRF and FM pain. In multivariate analyses adjusting for age, sex, and depressive symptoms, the association

between CSF CRF and sensory pain symptoms (t=2.54, p=0.027) persisted. Women with FM who reported a history of physical or sexual abuse had lower CSF CRF levels than women who did not report such a history. CSF CRF levels are associated with both pain symptoms and variation in autonomic function in FM. Differences in CSF CRF levels among women with and without a self-reported history of physical or sexual abuse suggest that subgroups of FM patients may exist with different neurobiological characteristics. Further studies are needed to better understand the nature of the association between CSF CRF and pain symptoms in FM

McNeil MM, Ma G, Aranas A, Payne DC, Rose CE, Jr. (2007) A comparative assessment of immunization records in the Defense Medical Surveillance System and the Vaccine Adverse Event Reporting System. Vaccine 25:3428-3436.
Abstract: We compared immunization data in the Defense Medical Surveillance System (DMSS) and immunization data for service members with an anthrax vaccine-associated adverse event reported to the Vaccine Adverse Event Reporting System (VAERS) during January 1998 through December 2004. Our main measure of agreement was sensitivity of the DMSS conditional on an immunization record(s) occurring in VAERS. The sensitivity of DMSS was 73% for all vaccines and 74% for the anthrax vaccine on the VAERS index immunization date. Our study is the first to quantify the agreement between immunization records in VAERS and DMSS. Our data suggest the immunization information in military VAERS reports and the DMSS is similar for anthrax and non-anthrax immunizations

Meyer DA, Shafer TJ (2006) Permethrin, but not deltamethrin, increases spontaneous glutamate release from hippocampal neurons in culture. Neurotoxicology 27:594-603.
Abstract: Pyrethroid insecticide modulation of the voltage-gated sodium channel (VGSC) is proposed to underlie their effects on neuronal excitability. However, some in vitro evidence indicates that target sites other than VGSCs could contribute to pyrethroid disruption of neuronal activity. VGSC-independent, pyrethroid-induced changes in neurotransmitter release were examined to investigate the possibility that target sites other than VGSCs contribute to pyrethroid effects. Using whole-cell patch clamp recordings, deltamethrin and permethrin effects on glutamate-mediated miniature excitatory postsynaptic currents (mEPSCs) from pyramidal neurons in mixed hippocampal cultures were examined. In the presence of the VGSC antagonist tetrodotoxin, the type I pyrethroid permethrin (10 µM) increased the average frequency of mEPSCs from a basal level of 1.0+/-0.4 to 3.5+/-0.6 Hz, with peak frequency of 9.9+/-1.5 Hz (n=6). Permethrin did not affect the distribution of current amplitudes, indicating that permethrin increased the probability of glutamate release at the presynaptic terminal without effects on postsynaptic responses. Removal of calcium from the extracellular solution following the induction of the permethrin-mediated effect decreased mEPSC frequency (6.8+/-1.8 Hz, n=3) to near control levels (1.9+/-0.8 Hz for control versus 2.5+/-0.6 Hz for permethrin minus Ca(2+), respectively). However, the N- and P/Q-type voltage-gated calcium channel antagonist omega-conotoxin MVIIC had no effect on the permethrin-dependent increase in mEPSC frequency. In contrast to permethrin, the type II pyrethroid deltamethrin (10 microM) failed to affect mEPSC frequency. These results indicate that permethrin causes a calcium-dependent increase in glutamate release from hippocampal neurons that is independent of effects on voltage-gated sodium or N- or P/Q-type voltage-gated calcium channels. The data indicate that permethrin increases mEPSC frequency via an alteration in intracellular calcium dynamics at the presynaptic terminal

Mihaylova I, DeRuyter M, Rummens JL, Bosmans E, Maes M (2007) Decreased expression of CD69 in chronic fatigue syndrome in relation to inflammatory markers: evidence for a severe disorder in the early activation of T lymphocytes and natural killer cells. Neuro Endocrinol Lett 28:477-483.
Abstract: There is some evidence that patients with chronic fatigue syndrome (CFS) suffer from immune abnormalities, such as immune activation and decreased immune cell responsivity upon polyclonal stimuli. This study was designed to evaluate lymphocyte activation in CFS by using a CD69 expression assay. CD69 acts as a costimulatory molecule for T- and natural killer (NK) cell activation. We collected whole blood from CFS patients, who met CDC [Centers for Disease Control and Prevention] criteria, and healthy volunteers. The blood samples were stimulated with mitogens during 18 h and the levels of activated T and NK cells expressing CD69 were measured on a Coulter Epics flow cytometer using a three color immunofluorescence staining protocol. The expression of the CD69 activation marker on T cells (CD3+, CD3+CD4+, and CD3+CD8+) and on NK cells (CD45+CD56+) was significantly lower in CFS patients than in healthy subjects. These differences were significant to the extent that a significant diagnostic performance was obtained, i.e., the area under the ROC curve was around 89%. No differences either in the number of leukocytes or in the number or percentage of lymphocytes, i.e., CD3, CD4, CD8 and CD19, could be found between CFS patients and the controls. Patients with CFS show defects in T- and NK cell activation. Since induction of CD69 surface expression is dependent on the activation of the protein kinase C (PKC) activation pathway, it is suggested that in CFS there is a disorder in the early activation of the immune system involving PKC

Morahan JM, Yu B, Trent RJ, Pamphlett R (2007) A gene-environment study of the paraoxonase 1 gene and pesticides in amyotrophic lateral sclerosis. Neurotoxicology 28:532-540.
Abstract: Sporadic amyotrophic lateral sclerosis (SALS) causes progressive muscle weakness because of the loss of motor neurons. SALS has been associated with exposure to environmental toxins, including pesticides and chemical warfare agents, many of which are organophosphates. The enzyme paraoxonase 1 (PON1) detoxifies organophosphates and the efficacy of this enzyme varies with polymorphisms in the PON1 gene. To determine if an impaired ability to break down organophosphates underlies some cases of SALS, we compared the frequencies of PON1 polymorphisms in SALS patients and controls and investigated gene-environment interactions with self-reported pesticide/herbicide exposure. The PON1 coding polymorphisms L55M, Q192R and I102V, and the promoter polymorphisms -909c>g, -832g>a, -162g>a and -108c>t, were genotyped in 143 SALS patients and 143 matched controls. Statistical comparisons were carried out at allele, genotype and haplotype levels. The PON1 promoter allele -108t, which reduces PON1 expression, was strongly associated with SALS. Overall, promoter haplotypes that decrease PON1 expression were associated with SALS, whereas haplotypes that increase expression were associated with controls. Coding polymorphisms did not correlate with SALS. Gene-environment interactions were identified at the allele level for some promoter SNPs and pesticide/herbicide exposure, but not at the genotype or haplotype level. In conclusion, some PON1 promoter polymorphisms may predispose to SALS, possibly by making motor neurons more susceptible to organophosphate-containing toxins

Morahan JM, Yu B, Trent RJ, Pamphlett R (2007) Genetic susceptibility to environmental toxicants in ALS. Am J Med Genet B Neuropsychiatr Genet 144:885-890.
Abstract: Environmental toxicants such as heavy metals, pesticides, and chemicals appear to be risk factors for sporadic amyotrophic lateral sclerosis (SALS). An impaired ability to break down these toxicants because of differences in detoxification genes could underlie some cases of this disease. We therefore examined the frequencies of single nucleotide polymorphisms (SNPs) in 186 SALS patients and 186 controls at the allele, genotype, and haplotype levels for the metallothionein (MT) family of genes, metal transcription factor-1 (MTF-1), and glutathione synthetase (GSS). Exposure to heavy metals, solvents/chemicals, and pesticides/herbicides was assessed by questionnaire, and gene-toxicant interactions were analyzed. An intronic SNP upstream of MT-Ie differed in SALS patients and controls at the allele and genotype levels. Haplotypes covering MT-I isoforms also differed between the two groups. Alleles and genotypes of one MTF-1 SNP differed in female SALS patients. One GSS haplotype interacted with both metals and solvents/chemicals to increase the risk of the disease. Differences in genes involved in handling toxicants, and interactions between toxicants and these genes, appear to be present in some patients with SALS. This suggests that impaired detoxification mechanisms play a role in SALS

Newton JL, Okonkwo O, Sutcliffe K, Seth A, Shin J, Jones DE (2007) Symptoms of autonomic dysfunction in chronic fatigue syndrome. QJM 100:519-526.
Abstract: BACKGROUND: Chronic fatigue syndrome (CFS) is common and its cause is unknown. AIM: To study the prevalence of autonomic dysfunction in CFS, and to develop diagnostic criteria. DESIGN: Cross-sectional study with independent derivation and validation phases. METHODS: Symptoms of autonomic dysfunction were assessed using the Composite Autonomic Symptom Scale (COMPASS). Fatigue was assessed using the Fatigue Impact Scale (FIS). Subjects were studied in two groups: phase 1 (derivation phase), 40 CFS patients and 40 age- and sex-matched controls; phase 2 (validation phase), 30 CFS patients, 37 normal controls and 60 patients with primary biliary cirrhosis. RESULTS: Symptoms of autonomic dysfunction were strongly and reproducibly associated with the presence of CFS or primary biliary cirrhosis (PBC), and correlated with severity of fatigue. Total COMPASS score >32.5 was identified in phase 1 as a diagnostic criterion for autonomic dysfunction in CFS patients, and was shown in phase 2 to have a positive predictive value of 0.96 (95%CI 0.86-0.99) and a negative predictive value of 0.84 (0.70-0.93) for the diagnosis of CFS. DISCUSSION: Autonomic dysfunction is strongly associated with fatigue in some, but not all, CFS and PBC patients. We postulate the existence of a 'cross-cutting' aetiological process of dysautonomia-associated fatigue (DAF). COMPASS >32.5 is a valid diagnostic criterion for autonomic dysfunction in CFS and PBC, and can be used to identify patients for targeted intervention studies

Niblett SH, King KE, Dunstan RH, Clifton-Bligh P, Hoskin LA, Roberts TK, Fulcher GR, McGregor NR, Dunsmore JC, Butt HL, Klineberg I, Rothkirch TB (2007) Hematologic and urinary excretion anomalies in patients with chronic fatigue syndrome. Exp Biol Med (Maywood) 232:1041-1049.
Abstract: Patients with chronic fatigue syndrome (CFS) have a broad and variable spectrum of signs and symptoms with variable onsets. This report outlines the results of a single-blind, cross-sectional research project that extensively investigated a large cohort of 100 CFS patients and 82 non fatigued control subjects with the aim of performing a case-

control evaluation of alterations in standard blood parameters and urinary amino and organic acid excretion profiles. Blood biochemistry and full blood counts were unremarkable and fell within normal laboratory ranges. However, the case-control comparison of the blood cell data revealed that CFS patients had a significant decrease in red cell distribution width and increases in mean platelet volume, neutrophil counts, and the neutrophil-lymphocyte ratio. Evaluation of the urine excretion parameters also revealed a number of anomalies. The overnight urine output and rate of amino acid excretion were both reduced in the CFS group ($P < 0.01$). Significant decreases in the urinary excretion of asparagine ($P < 0.0001$), phenylalanine ($P < 0.003$), the branch chain amino acids ($P < 0.005$), and succinic acid ($P < 0.0001$), as well as increases in 3-methylhistidine ($P < 0.05$) and tyrosine ($P < 0.05$) were observed. It was concluded that the urinary excretion and blood parameters data supported the hypothesis that alterations in physiologic homeostasis exist in CFS patients

Nilsen KB, Sand T, Westgaard RH, Stovner LJ, White LR, Bang LR, Helde G, Ro M (2007) Autonomic activation and pain in response to low-grade mental stress in fibromyalgia and shoulder/neck pain patients. Eur J Pain 11:743-755.
Abstract: OBJECTIVE: Psychosocial stress is a risk factor for musculoskeletal pain, but how stress affects musculoskeletal pain is poorly understood. We wanted to examine the relationship between low-grade autonomic activation and stress-related pain in patients with fibromyalgia and localised chronic shoulder/neck pain. METHODS: Twenty-three female patients with fibromyalgia, 29 female patients with chronic shoulder-neck pain, and 35 healthy women performed a stressful task lasting 60min. With a blinded study design, we recorded continuous blood pressure, heart rate, finger skin blood flow and respiration frequency before (10min), during (60min) and after (30min) the stressful task. The physiological responses were compared with subjective reports of pain. RESULTS: The increase in diastolic blood pressure and heart rate in response to the stressful task were smaller in fibromyalgia patients compared with the healthy controls. Furthermore, fibromyalgia patients had reduced finger skin blood flow at the end of the stressful task compared to healthy controls. We also found an inverse relationship between the heart rate response and development and recovery of the stress-related pain in fibromyalgia patients. CONCLUSION: We found abnormal cardiovascular responses to a 60min long stressful task in fibromyalgia patients. Furthermore, we found a negative association between the heart rate response and the pain which developed during the stressful task in the fibromyalgia group, possibly a result of reduced stress-induced analgesia for fibromyalgia patients

Oeh U, Andrasi A, Bouvier-Capely C, Carlan LD, Fischer H, Franck D, Hollriegl V, Li WB, Ritt J, Roth P, Schmitzer C, Wahl W, Zombori P (2007) Implementation of Bioassay Methods to Improve Assessment of Incorporated Radionuclides. Radiat Prot Dosimetry.
Abstract: The present work which was carried out in the framework of an EU project (IDEA: Internal Dosimetry--Enhancements in Application; Contract Number: FIKR CT2001 00164) shall provide commonly acceptable guidelines for optimum performance of ICP-MS measurements with focus on urinary measurements of uranium, thorium and actinides. From the results of this work it is recommended that, whenever feasible, 24 h urine sampling should be conducted to avoid large uncertainties in the quantitation of daily urinary excretion values. For storage, urine samples should be acidified and kept frozen before analysis. Measurement of total uranium in urine by ICP-MS at physiological levels (<10 ng/l) requires no sample preparation besides UV photolysis and/or dilution. For the measurement of thorium in urine by ICP-MS, it can be concluded, that salt removal from the urine samples is not recommended. For the measurement of actinides in urine it is shown that ICP-MS is well-suited and a good alternative to alpha-spectrometry for isotopes with T1/2 > 5 x 10(4) years. In general, ICP-MS measurements are an easy, fast and cost-saving methodology. New improved measuring techniques (HR-SF-ICP-MS) with detection limits in urine of 150 pg/1 (1.9 µBq/1) for ^{238}U, 30 pg/1 (2.4 µBq/l) for ^{235}U and 100 pg/l (0.4 µBq/1) for ^{232}Th, respectively, meet all necessary requirements. This method should therefore become the routine technique for incorporation monitoring of workers and of members of the general public, in particular for uranium contamination

Oeh U, Priest ND, Roth P, Ragnarsdottir KV, Li WB, Hollriegl V, Thirlwall MF, Michalke B, Giussani A, Schramel P, Paretzke HG (2007) Measurements of daily urinary uranium excretion in German peacekeeping personnel and residents of the Kosovo region to assess potential intakes of depleted uranium (DU). Sci Total Environ 381:77-87.
Abstract: Following the end of the Kosovo conflict, in June 1999, a study was instigated to evaluate whether there was a cause for concern of health risk from depleted uranium (DU) to German peacekeeping personnel serving in the Balkans. In addition, the investigations were extended to residents of Kosovo and southern Serbia, who lived in areas where DU ammunitions were deployed. In order to assess a possible DU intake, both the urinary uranium excretion of volunteer residents and water samples were collected and analysed using inductively coupled plasma-mass spectrometry (ICP-

MS). More than 1300 urine samples from peacekeeping personnel and unexposed controls of different genders and age were analysed to determine uranium excretion parameters. The urine measurements for 113 unexposed subjects revealed a daily uranium excretion rate with a geometric mean of 13.9 ng/d (geometric standard deviation (GSD)=2.17). The analysis of 1228 urine samples from the peacekeeping personnel resulted in a geometric mean of 12.8 ng/d (GSD=2.60). It follows that both unexposed controls and peacekeeping personnel excreted similar amounts of uranium. Inter-subject variation in uranium excretion was high and no significant age-specific differences were found. The second part of the study monitored 24 h urine samples provided by selected residents of Kosovo and adjacent regions of Serbia compared to controls from Munich, Germany. Total uranium and isotope ratios were measured in order to determine DU content. $^{235}U/^{238}U$ ratios were within +/-0.3% of the natural value, and $^{235}U/^{238}U$ was less than 2×10^{-7}, indicating no significant DU in any of the urine samples provided, despite total uranium excretion being relatively high in some cases. Measurements of ground and tap water samples from regions where DU munitions were deployed did not show any contamination with DU, except in one sample. It is concluded that both peacekeeping personnel and residents serving or living in the Balkans, respectively, were not exposed to significant amounts of DU

Patkar AA, Masand PS, Krulewicz S, Mannelli P, Peindl K, Beebe KL, Jiang W (2007) A randomized, controlled, trial of controlled release paroxetine in fibromyalgia. Am J Med 120:448-454.
Abstract: PURPOSE: We investigated the efficacy and tolerability of paroxetine controlled release, a selective serotonin reuptake inhibitor in fibromyalgia. METHODS: After excluding patients with current major depression and anxiety disorders, 116 subjects with fibromyalgia were enrolled in a 12-week, randomized, double-blind, placebo-controlled, trial of paroxetine controlled release (12.5-62.5 mg/day). The primary outcome measure was proportion of responders as defined as a> or =25% reduction in scores on the Fibromyalgia Impact Questionnaire (FIQ) from randomization to end of treatment. Secondary outcome measures included changes in FIQ scores, Clinical Global Impression - Improvement (CGI-I) and Severity (CGI-S) scores, Visual Analogue Scale for pain scores, number of tender points, and scores on the Sheehan Disability Scale (SDS). RESULTS: Significantly more patients in paroxetine controlled release group (57%) showed a> or =25% reduction in FIQ compared to placebo (33%) (P=.016). Paroxetine controlled release was significantly superior to placebo in reducing the FIQ total score (P =.015). The CGI-I ratings significantly favored the drug over placebo (P<.005). The improvements on other secondary outcome measures between the 2 groups were not statistically significant. Drowsiness, dry mouth, blurred vision, genital disorders, and anxiety were reported more frequently with paroxetine controlled release. The mean dose of paroxetine controlled release was 39.1 mg/day. CONCLUSIONS: Paroxetine controlled release appears to be well-tolerated and improve the overall symptomatology in patients with fibromyalgia without current mood or anxiety disorders. However, its effect on pain measures seems to be less robust

Payne DC, Rose CE, Jr., Aranas A, Zhang Y, Tolentino H, Weston E, McNeil MM, Ruscio B (2007) Assessment of anthrax vaccination data in the Defense Medical Surveillance System, 1998-2004. Pharmacoepidemiol Drug Saf 16:605-611.
Abstract: PURPOSE: Understanding the completeness and accuracy of U.S. military anthrax vaccination data is important to the design and interpretation of studies to assess the safety of anthrax vaccine. We estimated the agreement between electronically recorded anthrax vaccination data in the Defense Medical Surveillance System (DMSS) versus anthrax vaccination data abstracted from hardcopy medical charts in a representative sample of the U.S. military from 1998 to 2004. METHODS: Medical chart abstractions were conducted at 28 military treatment facilities for 4201 personnel. Abstracted anthrax vaccination data for 1817 personnel, representing 7400 anthrax vaccine doses, were compared with electronically captured data in the DMSS from 1998 to 2004. Sensitivity, positive predictive value (PPV), specificity and negative predictive value (NPV) were calculated using weighted analyses. RESULTS: Weighted person-level analysis revealed DMSS sensitivity = 93.8% (95%CI = 91.1, 95.8), specificity = 87.0% (79.0, 92.3), PPV = 85.6% (77.2, 91.3) and NPV = 94.5% (91.7, 96.4). Report of anthrax vaccination within a +/-7 days window in both medical chart and DMSS electronic data had a sensitivity of 88.3% (85.4, 90.7) and a PPV of 86.6% (84.9, 88.2) in the vaccine dose-level analysis. CONCLUSIONS: These results support that anthrax vaccination data captured by the DMSS are adequate for post-marketing surveillance investigations in the U.S. military and are of comparable quality to data captured by other vaccine safety databases

Pena-Philippides JC, Razani-Boroujerdi S, Singh SP, Langley RJ, Mishra NC, Henderson RF, Sopori ML (2007) Long- and short-term changes in the neuroimmune-endocrine parameters following inhalation exposures of F344 rats to low-dose sarin. Toxicol Sci 97:181-188.

Abstract: Inhalation of subclinical doses of sarin suppresses the antibody-forming cell (AFC) response, T-cell mitogenesis, and serum corticosterone (CORT) levels, and high doses of sarin cause lung inflammation. However, the duration of these changes is not known. In these studies, rats were exposed to a subclinical dose of sarin (0.4 mg/m3/h/day) for 1 or 5 days, and immune and inflammatory parameters were assayed up to 8 weeks before sarin exposure. Our results showed that the effects of a 5-day sarin exposure on the AFC response and T-cell receptor (TCR)-mediated Ca2+ response disappeared within 2-4 weeks after sarin exposure, whereas the CORT and adrenocorticotropin hormone (ACTH) levels remained significantly decreased. Pretreatment of rats with chlorisondamine attenuated the effects of sarin on the AFC and the TCR-mediated Ca2+ response, implicating the autonomic nervous system (ANS) in the sarin-induced changes in T-cell function. Moreover, exposure to a single or five repeated subclinical doses of sarin upregulated the mRNA expression of proinflammatory cytokines in the lung, which is associated with the activation of NF kappaB in bronchoalveolar lavage cells. These effects were lost within 2 weeks of sarin inhalation. Our results suggest that while sarin-induced changes in T cells and cytokine gene expression were short lived, suppression of CORT and ACTH levels were relatively long lived and might represent biomarkers of sarin exposure. Moreover, while the effects of sarin on T-cell function were regulated by the ANS, the decreased CORT levels by sarin might result from its effects on the hypothalamus-pituitary-adrenal axis

Petitot F, Frelon S, Moreels AM, Claraz M, Delissen O, Tourlonias E, Dhieux B, Maubert C, Paquet F (2007) Incorporation and distribution of uranium in rats after a contamination on intact or wounded skin. Health Phys 92:464-474.

Abstract: Uranium uptake can occur accidentally by inhalation, ingestion, injection, or absorption through intact or wounded skin. Intact or wounded skin routes of absorption of uranium have received little attention. The aims of our work were (1) to evaluate the influence of the type of wound contamination on the short term distribution and excretion of uranium in rats and (2) to generate data to assess the time available to treat contamination of intact or wounded skin before significant uptake of uranium occurs. Biokinetic data presented in the present paper are based on an in vivo rat model. This study shows that a significant uptake of a uranyl nitrate solution through intact skin can occur within the first 6 h of exposure. Absorption of a uranyl nitrate solution through excoriated skin is significant after only 30 min of exposure. After a 24-h exposure, uranium uptake through intact skin and excoriated skin represents about 0.4% and 38% of the initial deposit of uranium, respectively. Contaminated serious chemical skin burns induced by HNO3 or NaOH are paradoxically less important in terms of uranium uptake risk because 99% of the incorporated uranium remains trapped at the wound site and its incorporation is delayed for at least 6 h after the beginning of contamination. These results confirm that the biokinetics of a given physicochemical form of uranium incorporated after wound contamination depend largely on the physiological evolution of the considered wound. Each type of wound, with its corresponding biokinetics of a uranium species, is a particular case

Petrik MS, Wong MC, Tabata RC, Garry RF, Shaw CA (2007) Aluminum adjuvant linked to gulf war illness induces motor neuron death in mice. Neuromolecular Med 9:83-100.

Abstract: Gulf War illness (GWI) affects a significant percentage of veterans of the 1991 conflict, but its origin remains unknown. Associated with some cases of GWI are increased incidences of amyotrophic lateral sclerosis and other neurological disorders. Whereas many environmental factors have been linked to GWI, the role of the anthrax vaccine has come under increasing scrutiny. Among the vaccine's potentially toxic components are the adjuvants aluminum hydroxide and squalene. To examine whether these compounds might contribute to neuronal deficits associated with GWI, an animal model for examining the potential neurological impact of aluminum hydroxide, squalene, or aluminum hydroxide combined with squalene was developed. Young, male colony CD-1 mice were injected with the adjuvants at doses equivalent to those given to US military service personnel. All mice were subjected to a battery of motor and cognitive-behavioral tests over a 6-mo period postinjection. Following sacrifice, central nervous system tissues were examined using immunohistochemistry for evidence of inflammation and cell death. Behavioral testing showed motor deficits in the aluminum treatment group that expressed as a progressive decrease in strength measured by the wire-mesh hang test (final deficit at 24 wk; about 50%). Significant cognitive deficits in water-maze learning were observed in the combined aluminum and squalene group (4.3 errors per trial) compared with the controls (0.2 errors per trial) after 20 wk. Apoptotic neurons were identified in aluminum-injected animals that showed significantly increased activated caspase-3 labeling in lumbar spinal cord (255%) and primary motor cortex (192%) compared with the

controls. Aluminum-treated groups also showed significant motor neuron loss (35%) and increased numbers of astrocytes (350%) in the lumbar spinal cord. The findings suggest a possible role for the aluminum adjuvant in some neurological features associated with GWI and possibly an additional role for the combination of adjuvants

Raskind MA, Peskind ER, Hoff DJ, Hart KL, Holmes HA, Warren D, Shofer J, O'Connell J, Taylor F, Gross C, Rohde K, McFall ME (2007) A parallel group placebo controlled study of prazosin for trauma nightmares and sleep disturbance in combat veterans with post-traumatic stress disorder. Biol Psychiatry 61:928-934. (DoD-166)
Abstract: BACKGROUND: Excessive brain responsiveness to norepinephrine appears to contribute to post-traumatic stress disorder (PTSD), particularly at night. Prazosin, a brain active alpha-1 adrenergic receptor antagonist, significantly reduced trauma nightmares and sleep disturbance in 10 Vietnam War combat veterans in a previous placebo-controlled crossover study. The current parallel group trial in a larger sample of veterans evaluated prazosin effects on trauma nightmares, sleep quality, global clinical status, dream characteristics, and comorbid depression. METHODS: Forty veterans (mean age 56 +/- 9) with chronic PTSD and distressing trauma nightmares and sleep disturbance were randomized to evening prazosin (13.3 +/- 3 mg/day) or placebo for 8 weeks. RESULTS: In the evaluable sample (n = 34), primary outcome measures demonstrated that prazosin was significantly superior to placebo for reducing trauma nightmares and improving sleep quality and global clinical status with large effect sizes. Prazosin shifted dream characteristics from those typical of trauma-related nightmares toward those typical of normal dreams. Blood pressure changes from baseline to end study did not differ significantly between prazosin and placebo. CONCLUSIONS: Prazosin is an effective and well-tolerated treatment for trauma nightmares, sleep disturbance and global clinical status in veterans with chronic PTSD

Reeves WC, Jones JF, Maloney E, Heim C, Hoaglin DC, Boneva RS, Morrissey M, Devlin R (2007) Prevalence of chronic fatigue syndrome in metropolitan, urban, and rural Georgia. Popul Health Metr 5:5.
Abstract: BACKGROUND: Chronic fatigue syndrome (CFS) is a debilitating illness with no known cause or effective therapy. Population-based epidemiologic data on CFS prevalence are critical to put CFS in a realistic context for public health officials and others responsible for allocating resources. METHODS: Based on a random-digit dialing survey we ascertained CFS cases and controls to estimate the prevalence of CFS in metropolitan, urban, and rural populations of Georgia. This report focuses on the 5,623 of 19,381 respondents ages 18 to 59 years old. Fatigued (2,438), randomly selected unwell not fatigued (1,429) and randomly selected well (1,756) respondents completed telephone questionnaires concerning fatigue, other symptoms, and medical history. Subsets of those identified by interview as having CFS-like illness (292), chronic unwellness which was not CFS-like (268 - randomly selected), and well subjects (223, matched to those with CFS-like illness on sex, race, and age) completed a clinical evaluation. RESULTS: We estimated that 2.54% of persons 18 to 59 years of age suffered from CFS. There were no significant differences in prevalence of CFS between metropolitan, urban or rural populations or between white and black residents of the three regions. However, there were significant differences in female-to-male ratios of prevalence across the strata (metropolitan female: male 11.2 : 1, urban 1.7 : 1, rural 0.8 : 1). CONCLUSION: We estimated that 2.54% of the Georgia population suffers from CFS, which is 6- to 10-fold higher than previous population-based estimates in other geographic areas. These differences may reflect broader screening criteria and differences in the application of the case definition. However, we cannot exclude the possibility that CFS prevalence may be higher in Georgia than other areas where it has been measured. Although the study did not identify differences in overall prevalence between metropolitan, urban, and rural Georgia populations, it did suggest the need for additional stratified analyses by geographic strata

Richards RS, Wang L, Jelinek H (2007) Erythrocyte oxidative damage in chronic fatigue syndrome. Arch Med Res 38:94-98.
Abstract: BACKGROUND: It has been hypothesized that a link exists between erythrocyte metabolism (particularly redox metabolism) and erythrocyte shape and that both are related to erythrocyte deformability. The aim of this research is to confirm the results of earlier studies and to investigate a correlation between erythrocyte morphology and erythrocyte oxidative damage in chronic fatigue syndrome (CFS). METHODS: Reduced glutathione (GSH), malondialdehyde (MDA), methemoglobin (metHb) and 2,3-diphosphoglyceric acid (2,3-DPG) were measured in 31 patients suffering from CFS and 41 healthy control subjects. Scanning electron microscopic studies of the erythrocytes from both groups were also carried out. RESULTS: There was evidence of oxidative damage in CFS with statistically significant increases in 2,3-DPG ($p < 0.05$), metHb ($p < 0.005$) and MDA ($p < 0.01$). The CFS patients in this study also had significantly more stomatocytes in their blood than the normal subjects ($p < 0.005$). CONCLUSIONS: There is

a strong likelihood that the increase in erythrocyte antioxidant activity is associated with the presence of stomatocytes. The results of this study provide further evidence for the role of free radicals in the pathogenesis of CFS and a link between erythrocyte metabolism and erythrocyte shape

Riddle JR, Smith TC, Smith B, Corbeil TE, Engel CC, Wells TS, Hoge CW, Adkins J, Zamorski M, Blazer D (2007) Millennium Cohort: the 2001-2003 baseline prevalence of mental disorders in the U.S. military. J Clin Epidemiol 60:192-201. (DoD-143)

Abstract: OBJECTIVES: The 12-month prevalence of common mental illnesses in the United States is estimated to be 26%, accounting for an increasing fraction of all disability in the general population. The U.S. military is a unique group involved in response and defense during times of conflicts and disasters. The mental health of service members affects organizational productivity and effectiveness and is of great importance to the health of U.S. military members and public health in general. STUDY DESIGN AND SETTING: In the present report, the authors describe the baseline prevalence of mental disorders in a large U.S. military cohort, the Millennium Cohort, established for a 22-year longitudinal study of the health effects of military service. Using crude and weighted prevalence and multivariable logistic regression, the mental health morbidity of the Millennium Cohort is reported for various demographics. RESULTS: These analyses suggest that although the cohort compares favorably to other populations, there are military subpopulations, including women, younger, less educated, single, white, short-term service, enlisted, and Army members, who are at greater odds for some mental disorders. CONCLUSION: With ongoing U.S. involvement in combat operations around the world, these baseline data are essential to assessing long-term mental health morbidity in U.S. military service members

Rona RJ, Fear NT, Hull L, Wessely S (2007) Women in novel occupational roles: mental health trends in the UK Armed Forces. Int J Epidemiol 36:319-326.

Abstract: BACKGROUND: There is uncertainty about whether women in the military have more psychological symptoms than men and whether psychological symptoms have increased over time. The aims of this study were to assess changes in psychological symptoms in military women over time, to compare them with men, and assess the effect of deployment. METHODS: Two cross-sectional studies based on random samples of the Armed Forces were used to assess the effects of deployment to the Gulf and Iraq Wars. We selected for the analyses all the women and a 20% random sample of men who completed a questionnaire stratified by rank. We assessed psychological distress, number of symptoms, post-traumatic stress reaction (PTSR), chronic fatigue and alcohol misuse. RESULTS: There has been an increase in psychological symptoms, including alcohol misuse, in those not deployed to the Gulf or Iraq Wars, especially in women. The odds ratios for PTSR [5.82 (95% CI: 1.27-26.71)], multiple symptoms [8.49 (1.97-36.65)] and alcohol misuse [6.20 (2.09-18.37)] were higher in women than in men in the non-deployed samples. Psychological distress and chronic fatigue was more common in women, and alcohol misuse, was more common in men. In women, psychological symptoms were positively associated with deployment in the Gulf War, but not the Iraq War. CONCLUSION: Psychological symptoms in the Armed Forces have increased over time regardless of gender, in those not deployed. The association between gender and psychological symptoms has not changed over time. The deployment effect in women is similar to that described in men

Ryan MA, Smith TC, Smith B, Amoroso P, Boyko EJ, Gray GC, Gackstetter GD, Riddle JR, Wells TS, Gumbs G, Corbeil TE, Hooper TI (2007) Millennium Cohort: enrollment begins a 21-year contribution to understanding the impact of military service. J Clin Epidemiol 60:181-191. (DoD-143)

Abstract: OBJECTIVE: In response to health concerns of military members about deployment and other service-related exposures, the Department of Defense (DoD) initiated the largest prospective study ever undertaken in the U.S. military. STUDY DESIGN AND SETTING: The Millennium Cohort uses a phased enrollment strategy to eventually include more than 100,000 U.S. service members who will be followed up through the year 2022, even after leaving military service. Subjects will be linked to DoD and Veterans Affairs databases and surveyed every 3 years to obtain objective and self-reported data on exposures and health outcomes. RESULTS: The first enrollment phase was completed in July 2003 and resulted in 77,047 consenting participants, well representative of both active-duty and Reserve/Guard forces. This report documents the baseline characteristics of these Cohort members, describes traditional, postal, and Web-based enrollment methods; and describes the unique challenges of enrolling, retaining, and following such a large Cohort. CONCLUSION: The Millennium Cohort was successfully launched and is becoming especially relevant, given current deployment and exposure concerns. The Cohort is representative of the U.S. military and promises to provide new insight into the long-term effects of military occupations on health for years to come

Sava V, Reunova O, Velasquez A, Sanchez-Ramos J (2006) Can low level exposure to ochratoxin-A cause parkinsonism? J Neurol Sci 249:68-75.
Abstract: Mycotoxins are fungal metabolites with pharmacological activities that have been utilized in the production of antibiotics, growth promoters, and other classes of drugs. Some mycotoxins have been developed as biological and chemical warfare agents. Bombs and ballistic missiles loaded with aflatoxin were stockpiled and may have been deployed by Iraq during the first Gulf War. In light of the excess incidence of amyotrophic lateral sclerosis (ALS) in veterans from Operation Desert Storm, the potential for delayed neurotoxic effects of low doses of mycotoxins should not be overlooked. Ochratoxin-A (OTA) is a common mycotoxin with complex mechanisms of action, similar to that of the aflatoxins. Acute administration of OTA at non-lethal doses (10% of the LD(50)) have been shown to increase oxidative DNA damage in brain up to 72 h, with peak effects noted at 24 h in midbrain (MB), caudate/putamen (CP) and hippocampus (HP). Levels of dopamine (DA) and its metabolites in the striatum (e.g., CP) were shown to be decreased in a dose-dependent manner. The present study focused on the effects of chronic low dose OTA exposure on regional brain oxidative stress and striatal DA metabolism. Continuous administration of low doses of OTA with implanted subcutaneous Alzet minipumps caused a small but significant decrease in striatal DA levels and an upregulation of anti-oxidative systems and DNA repair. It is possible that low dose exposure to OTA will result in an earlier onset of parkinsonism when normal age-dependent decline in striatal DA levels are superimposed on the mycotoxin-induced lesion

Schmidt-Wilcke T, Luerding R, Weigand T, Jurgens T, Schuierer G, Leinisch E, Bogdahn U (2007) Striatal grey matter increase in patients suffering from fibromyalgia--a voxel-based morphometry study. Pain 132 Suppl 1:S109-S116.
Abstract: Fibromyalgia (FM), among other chronic pain syndromes, such as chronic tension type headache and atypical face pain, is classified as a so-called dysfunctional pain syndrome. Patients with fibromyalgia suffer from widespread, "deep" muscle pain and often report concomitant depressive episodes, fatigue and cognitive deficits. Clear evidence for structural abnormalities within the muscles or soft tissue of fibromyalgia patients is lacking. There is growing evidence that clinical pain in fibromyalgia has to be understood in terms of pathological activity of central structures involved in nociception. We applied MR-imaging and voxel-based morphometry, to determine whether fibromyalgia is associated with altered local brain morphology. We investigated 20 patients with the diagnosis of primary fibromyalgia and 22 healthy controls. VBM revealed a conspicuous pattern of altered brain morphology in the right superior temporal gyrus (decrease in grey matter), the left posterior thalamus (decrease in grey matter), in the left orbitofrontal cortex (increase in grey matter), left cerebellum (increase in grey matter) and in the striatum bilaterally (increase in grey matter). Our data suggest that fibromyalgia is associated with structural changes in the CNS of patients suffering from this chronic pain disorder. They might reflect either a consequence of chronic nociceptive input or they might be causative to the pathogenesis of fibromyalgia. The affected areas are known to be both, part of the somatosensory system and part of the motor system

Sharma A, Williams K, Raja SN (2006) Advances in treatment of complex regional pain syndrome: recent insights on a perplexing disease. Curr Opin Anaesthesiol 19:566-572.
Abstract: PURPOSE OF REVIEW: The paper is a critical appraisal of recent advances in the treatment of complex regional pain syndrome. Rapidly changing concepts related to the pathophysiology of this disease has transformed its current management and necessitates an updated review of the literature. RECENT FINDINGS: Chronic regional pain syndrome is a perplexing disease that continues to challenge researchers with respect to its cause and treatment. Recent modification to diagnostic criteria has enabled clinicians to diagnose this disease in a more consistent fashion. Emerging data indicate a possible role of inflammation in the overall pathophysiology and have led to treatment trials with newer anti-inflammatory medications. Certain 'conventional' interventional techniques have been recently scrutinized. A few novel therapeutic options like graded imagery are also outlined. SUMMARY: Enhanced insight into the pathophysiology of chronic regional pain syndrome has modified current clinical practice and the focus of research. Certain 'standard' therapeutic options for chronic regional pain syndrome have failed the test of time while others have prevailed. New options have recently been evaluated and have shown promising early results. Knowledge of recent advances in chronic regional pain syndrome will help pain physicians provide optimal care to these patients

Sirivarasai J, Kaojarern S, Yoovathaworn K, Sura T (2007) Paraoxonase (PON1) polymorphism and activity as the determinants of sensitivity to organophosphates in human subjects. Chem Biol Interact 168:184-192.
Paraoxonase (PON1) plays an important role in mechanism of organophosphorus compound (OP) toxicity, as seen both in vitro and in vivo studies. Polymorphisms of PON1 gene at coding and promoter regions have also been to affect on the hydrolytic activity and PON1 level. The objectives of this study were to determine PON1 polymorphism and

activity in an OP-exposed population and the effects on inhibition of cholinesterase activity. The studied population consisted of control (n=30) and exposed groups (n=90). All enzyme activities (AChE, BuChE, paraoxonase, arylesterase and diazonase) were measured once for control group and two periods of exposure for exposed group. Three polymorphisms of PON1 (Q192R, L55M and T-108C) were identified only in the exposed subjects. The results demonstrated that AChE activity in both high (345.5 µkat/gHb) and low exposure periods (496.9 µkat/gHb) of the exposed group were significantly different from control group (649.7 µkat/gHb, $p<0.01$). For BuChE activity, the exposed group also showed the statistically lower level in both periods (high exposure period: 62.17 µkat/L and low exposure period: 81.84 µkat/L) than those in the control group (93.35 microkat/L). Serum paraoxonase activity was significantly different among individual genotypes, RR>QR>RR, LL>LM and -108CC>-108CT>-108TT, but this was not found for those of arylesterase and diazonase activities. Q192R and L55M as well as Q192R and T-108C also presented substantial linkage disequilibrium. Further analysis was performed with haplotypes and various enzyme activities. AChE activity was not affected by haplotypes. Individuals with "211" haplotype showed significantly higher paraoxonase activity and BuChE activity than other haplotypes but not in diazonase activity. In conclusion, PON1 gene exhibited a wide variation in enzyme activities both within and between genotypes which implied insights of a potentially difference in sensitivity to OP toxicity

Smith AP, Lee NM (2007) Role of zinc in ALS. Amyotroph Lateral Scler 8:131-143.
Abstract: The causes of amyotrophic lateral sclerosis (ALS) are poorly understood. A small proportion, about 2%, is associated with a mutation in the superoxide dismutase (SOD1) gene, and mice expressing this mutant gene exhibit a progressive, ALS-like neurodegenerative disease. Studies of these animals, as well as of human post mortem tissue, reveal the presence of multiple pathological processes, including oxidative stress, glutamate excitotoxicity, neuroinflammation, mitochondrial degeneration, alterations in neurofilaments and neurotubules, mitochondrial damage, aggregation of proteins, abnormalities in growth factors, and apoptosis. We propose that alterations in the disposition of zinc ions may be important in the initiation and development of ALS. SOD1 binds zinc, and many of the mutant forms of this enzyme associated with ALS show altered zinc binding. Alterations in the expression of metallothioneins (MTs), which regulate cellular levels of zinc, have been reported in mutant SOD1 mice, and deletion of MTs in these animals accelerates disease progression. Zinc plays a key role in all the pathological processes associated with ALS. Our zinc hypothesis also may help explain evidence for environmental factors in some cases of ALS, such as in the Chamorro tribe in Guam and in the Gulf War

Smith B, Leard CA, Smith TC, Reed RJ, Ryan MA (2007) Anthrax vaccination in the Millennium Cohort: validation and measures of health. Am J Prev Med 32:347-353. (DoD-143)
Abstract: BACKGROUND: In 1998, the United States Department of Defense initiated the Anthrax Vaccine Immunization Program. Concerns about vaccine-related adverse health effects followed, prompting several studies. Although some studies used self-reported vaccination data, the reliability of such data has not been established. The purpose of this study was to compare self-reported anthrax vaccination to electronic vaccine records among a large military cohort and to evaluate the relationship between vaccine history and health outcome data. METHODS: Between September 2005 and February 2006 self-reported anthrax vaccination was compared to electronic records for 67,018 participants enrolled in the Millennium Cohort Study between 2001 and 2003 using kappa statistics. Multivariable modeling investigated vaccination concordance as it pertains to subjective health (functional status) and objective health (hospitalization) metrics. RESULTS: Greater than substantial agreement (kappa=0.80) was found between self-report and electronic recording of anthrax vaccination. Of all participants with electronic documentation of anthrax vaccination, 98% self-reported being vaccinated; and of all participants with no electronic record of vaccination, 90% self-reported not receiving a vaccination. There were no differences between vaccinated and unvaccinated participants in overall measures of health. Only the subset of participants who self-reported anthrax vaccination, but had no electronic confirmation, differed from others in the cohort, with consistently lower measures of health as indicated by Medical Outcomes Study 36-Item Short Form Health Survey for Veterans (SF-36V) scores. CONCLUSIONS: These results indicate that military members accurately recall their anthrax vaccinations. Results also suggest that anthrax vaccination among Millennium Cohort participants is not associated with self-reported health problems or broad measures of health problems severe enough to require hospitalization. Service members who self-report vaccination with no electronic documentation of vaccination, however, report lower measures of physical and mental health and deserve further research

Stimpson NJ, Unwin C, Hull L, David T, Wessely S, Lewis G (2006) Prevalence of reported pain, widespread pain, and pain symmetry in veterans of the Persian Gulf War (1990-1991): the use of pain manikins in Persian Gulf War health research. Mil Med 171:1181-1186.
Abstract: The reporting of pain was compared for U.K. Persian Gulf War veterans, veterans from the Bosnian conflict, and personnel employed in the military at the time of the Persian Gulf War but not deployed (era comparison group). Pain manikins were used to assess the prevalence of the reporting of pain in different body sites and the prevalence of the reporting of widespread pain, in relation to comparison samples. Data from > 8,195 veterans were collected from a previously reported, cross-sectional, population-based, postal questionnaire survey. A greater proportion of Persian Gulf War veterans reported pain in the majority of the 25 areas of the body, compared with the Bosnia and era comparison groups. A greater proportion of Persian Gulf War veterans also fulfilled American College of Rheumatology criteria for widespread pain, compared with the Bosnia and era comparison groups (odds ratio, 1.82; 95% confidence interval, 1.51-2.20). Participants were much more likely to report pain in an opposite limb if pain was reported in the first limb (odds ratio, 36.9; 95% confidence interval, 31.7-43.0). Widespread pain was also more prevalent in the Persian Gulf War veteran sample compared to the comparison groups. Several years after the end of the Persian Gulf War, veterans still report pain. The mechanisms of this remain unclear. Implications for baseline monitoring of the health of military personnel are discussed

Tanriverdi F, Karaca Z, Unluhizarci K, Kelestimur F (2007) The hypothalamo-pituitary-adrenal axis in chronic fatigue syndrome and fibromyalgia syndrome. Stress 10:13-25.
Abstract: The hypothalamo-pituitary-adrenal (HPA) axis plays a major role in the regulation of responses to stress. Human stress-related disorders such as chronic fatigue syndrome (CFS), fibromyalgia syndrome (FMS), chronic pelvic pain and post-traumatic stress disorder are characterized by alterations in HPA axis activity. However, the role of the HPA axis alterations in these stress-related disorders is not clear. Most studies have shown that the HPA axis is underactive in the stress-related disorders, but contradictory results have also been reported, which may be due to the patients selected for the study, the methods used for the investigation of the HPA axis, the stage of the syndrome when the tests have been done and the interpretation of the results. There is no structural abnormality in the endocrine organs which comprise the HPA axis, thus it seems that hypocortisolemia found in the patients with stress-related disorder is functional. It may be also an adaptive response of the body to chronic stress. In this review, tests used in the assessment of HPA axis function and the HPA axis alterations found in CFS and FMS are discussed in detail

Terry AV, Jr., Gearhart DA, Beck WD, Jr., Truan JN, Middlemore ML, Williamson LN, Bartlett MG, Prendergast MA, Sickles DW, Buccafusco JJ (2007) Chronic, intermittent exposure to chlorpyrifos in rats: protracted effects on axonal transport, neurotrophin receptors, cholinergic markers, and information processing. J Pharmacol Exp Ther 322:1117-1128.
Abstract: Persistent behavioral abnormalities have been commonly associated with acute organophosphate (OP) pesticide poisoning; however, relatively little is known about the consequences of chronic OP exposures that are not associated with acute cholinergic symptoms. In this study, the behavioral and neurochemical effects of chronic, intermittent, and subthreshold exposures to the OP pesticide, chlorpyrifos (CPF), were investigated. Rats were injected with CPF s.c. (dose range, 2.5-18.0 mg/kg) every other day over the course of 30 days and then were given a 2-week CPF-free washout period. In behavioral experiments conducted during the washout period, dose-dependent decrements in a water-maze hidden platform task and a prepulse inhibition procedure were observed, without significant effects on open-field activity, Rotorod performance, grip strength, or a spontaneous novel object recognition task. After washout, levels of CPF and its metabolite 3,5,6-trichloro-2-pyridinol were minimal in plasma and brain; however, cholinesterase inhibition was still detectable. Furthermore, the 18.0 mg/kg dose of CPF was associated with (brain region-dependent) decreases in nerve growth factor receptors and cholinergic proteins including the vesicular acetylcholine transporter, the high-affinity choline transporter, and the α-(7)-nicotinic acetylcholine receptor. These deficits were accompanied by decreases in anterograde and retrograde axonal transport measured in sciatic nerves ex vivo. Thus, low-level (intermittent) exposure to CPF has persistent effects on neurotrophin receptors and cholinergic proteins, possibly through inhibition of fast axonal transport. Such neurochemical changes may lead to deficits in information processing and cognitive function

The GK, Bleijenberg G, van der Meer JW (2007) The Effect of Acclydine in Chronic Fatigue Syndrome: a Randomized Controlled Trial. PLoS Clin Trials 2:e19.
Abstract: OBJECTIVES: It is unclear whether insulin-like growth factor (IGF) function is involved in the pathophysiology of chronic fatigue syndrome (CFS). Unpublished data and reports in patient organization newsletters suggest that Acclydine, a food supplement, could be effective in the treatment of CFS by increasing biologically active

IGF1 levels. Here we aimed to measure the IGF1 and IGF binding protein (IGFBP) 3 status of CFS patients compared to age- and gender-matched neighborhood controls, and to assess the effect of Acclydine on fatigue severity, functional impairment, and biologically active IGF1 level (IGFBP3/IGF1 ratio). DESIGN: A randomized, placebo-controlled, double-blind clinical trial. SETTING: Radboud University Nijmegen Medical Centre, The Netherlands. PARTICIPANTS: Fifty-seven adult patients who fulfilled the US Centers for Disease Control and Prevention criteria for CFS. IGF status of 22 CFS patients was compared to that of 22 healthy age- and gender-matched neighborhood control individuals. INTERVENTION: Acclydine or placebo for 14 wk. OUTCOME MEASURES: Outcomes were fatigue severity (Checklist Individual Strength, subscale fatigue severity [CIS-fatigue]), functional impairment (Sickness Impact Profile-8 [SIP-8]), and biologically active IGF1 serum concentrations. Analyses were on an intention-to-treat basis. RESULTS: There was no difference in IGF status in 22 CFS patients compared to healthy age- and gender-matched control individuals. Treatment with Acclydine did not result in significant differences compared with the placebo group on any of the outcome measures: CIS-fatigue +1.1 (95% CI -4.4 to +6.5, p = 0.70), SIP-8 +59.1 (95% CI -201.7 to +319.8, p = 0.65), and IGFBP3/IGF1 ratio -0.5 (95% CI -2.8 to +1.7, p = 0.63). CONCLUSION: We found no differences in IGF1 status in CFS patients compared to healthy matched neighborhood controls. In addition, the results of this clinical trial do not demonstrate any benefit of Acclydine over placebo in the treatment of CFS

Thiebault C, Carriere M, Milgram S, Simon A, Avoscan L, Gouget B (2007) Uranium induces apoptosis and is genotoxic to normal rat kidney (NRK-52E) proximal cells. Toxicol Sci 98:479-487.
Abstract: Uranium (U) is a heavy metal used in the nuclear industry and for military applications. U compounds are toxic. Their toxicity is mediated either by their radioactivity or their chemical properties. Mammalian kidneys and bones are the main organs affected by U toxicity. Although the most characteristic response to U exposure is renal dysfunction, little information is available on the mechanisms of its toxicity at the molecular level. This report studied the genotoxicity of U. Apoptosis induction in normal rat kidney (NRK-52(E)) proximal cells was investigated as a function of exposure time or concentrations (0-800 µM). In parallel, DNA damage was evaluated by several methods. In order to distinguish between the intrinsic and the extrinsic pathways of apoptosis, caspases-8, -9, -10 assays were conducted and the mitochondrial membrane potential was measured. Three methods were selected for their complementarities in the detection of genetic lesions. The comet assay was used for the detection of primary lesions of DNA. gamma-H2AX immunostaining was achieved to detect DNA double-strand breaks. The micronucleus assay was used to detect chromosomic breaks or losses. DNA damage and apoptosis were observed in a concentration-dependent manner. This study demonstrated that U is genotoxic from 300 µM and induces caspase-dependent apoptosis cell death from 200 µM mainly through the intrinsic pathway in NRK-52(E) cells. These results suggest that the DNA damage caused by U is reversible at low concentration (200-400 µM) but becomes irreversible and leads to cell death for higher concentrations (500-800 µM)

Toomey R, Kang HK, Karlinsky J, Baker DG, Vasterling JJ, Alpern R, Reda DJ, Henderson WG, Murphy FM, Eisen SA (2007) Mental health of US Gulf War veterans 10 years after the war. Br J Psychiatry 190:385-393.
Abstract: BACKGROUND: Gulf War veterans reported multiple psychological symptoms immediately after the war; the temporal course of these symptoms remains unclear. AIMS: To assess the prevalence of war era onset mental disorders in US veterans deployed to the Gulf War and in non-deployed veterans 10 years after the war. METHOD: Mental disorders were diagnosed using structured clinical interviews. Standard questionnaires assessed symptoms and quality of life. RESULTS: Gulf War-era onset mental disorders were more prevalent in deployed veterans (18.1%, n=1061) compared with non-deployed veterans (8.9%, n=1128). The prevalence of depression and anxiety declined 10 years later in both groups, but remained higher in the deployed group, who also reported more symptoms and a lower quality of life than the non-deployed group. Remission of depression may be related to the presence of comorbid psychiatric disorders and level of education. Remission of anxiety was related to treatment with medication. CONCLUSIONS: Gulf War deployment was associated with an increased prevalence of mental disorders, psychological symptoms and a lower quality of life beginning during the war and persisting at a lower rate 10 years later

Vietti KR, Lasley SM (2007) Stimulus-evoked glutamate release is diminished by acute exposure to uranium in vitro. Neurotoxicol Teratol 29:607-612.
Abstract: Uranium is used in civilian applications, in the manufacture of nuclear fuel, and by the military for munitions and armament, but little information is available on its neurotoxicity. Neurological dysfunctions have been observed after chronic exposure in both animals and humans, but the actions of acute exposure on amino acid neurotransmission have not been investigated. The following study was performed to examine the effects of uranyl ion (UO_2^{+2}) on hippocampal glutamatergic and GABAergic function as possible bases for the neurotoxicity and to assess the direct

effects on the exocytotic process. Nominal UO_2^{+2} concentrations were applied to superfused hippocampal synaptosomes to permit estimation of the metal's potency on endogenous transmitter release in the presence and absence of Ca^{+2}. K^+-evoked glutamate release was diminished in the range of 10 nM-316 µM UO_2^{+2}, resulting in an IC_{50} of 1.92 µM. In contrast, the potency of UO_2^{+2} to decrease stimulated GABA release was reduced, producing an IC_{50} approximately 2.6 mM. In the absence of Ca^{+2} in the superfusion medium there was no systematic change in the magnitude of glutamate or GABA release, suggesting that UO_2^{+2} does not possess Ca^{+2}-mimetic properties. The inhibitory potency of UO_2^{+2} on glutamate release is similar to the potencies of other multivalent metal ions, suggesting by inference an action exerted on voltage-sensitive Ca^{+2} channels. The bases for the reduced potency to inhibit GABA release is not known, but differential sensitivity to other heavy metals has been reported for glutamate and GABA neurotransmission. These findings indicate a profile of neurotoxicity not unlike that of other metal ions, and indicate the importance of extending subsequent studies to chronic exposure models

Vogt DS, Tanner LR (2007) Risk and resilience factors for posttraumatic stress symptomatology in Gulf War I veterans. J Trauma Stress 20:27-38.
Abstract: What factors distinguish war-exposed veterans who experience posttraumatic stress symptomatology (PTSS) from those who do not? This study used structural equation modeling procedures to examine the complex interplay among predeployment, war-zone, and postdeployment factors as they relate to PTSS in a sample of Gulf War I veterans. A primary goal was to determine to what extent previously documented associations among Vietnam veterans would replicate in this more contemporary veteran cohort. Results supported a multivariate etiological perspective on PTSS, with war-zone factors accounting for the largest proportion of variance in PTSS. The majority of hypothesized associations held, suggesting that the mechanisms underlying PTSS may be similar across veteran cohorts

Whalley CE, McGuire JM, Miller DB, Jakubowski EM, Mioduszewski RJ, Thomson SA, Lumley LA, McDonough JH, Shih TM (2007) Kinetics of sarin (GB) following a single sublethal inhalation exposure in the guinea pig. Inhal Toxicol 19:667-681.
Abstract: To improve toxicity estimates from sublethal exposures to chemical warfare nerve agents (CWNA), it is necessary to generate mathematical models of the absorption, distribution, and elimination of nerve agents. However, current models are based on representative data sets generated with different routes of exposure and in different species and are designed to interpolate between limited laboratory data sets to predict a wide range of possible human exposure scenarios. This study was performed to integrate CWNA sublethal toxicity data in male Duncan Hartley guinea pigs. Specific goal was to compare uptake and clearance kinetics of different sublethal doses of sarin (either 0.1 x or 0.4 x LC50) in blood and tissues of guinea pigs exposed to agent by acute whole-body inhalation exposure after the 60-min LC50 was determined. Arterial catheterization allowed repeated blood sampling from the same animal at various time periods. Blood and tissue levels of acetylcholinesterase, butyrylcholinesterase, and regenerated sarin (rGB) were determined at various time points during and following sarin exposure. The following pharmacokinetic parameters were calculated from the graph of plasma or RBC rGB concentration versus time: time to reach the maximal concentration; maximal concentration; mean residence time; clearance; volume of distribution at steady state; terminal elimination-phase rate constant; and area under plasma concentration time curve extrapolated to infinity using the WinNonlin analysis program 5.0. Plasma and RBC t(1/2) for rGB was also calculated. Data will be used to develop mathematical model of absorption and distribution of sublethal sarin doses into susceptible tissues

Wingenfeld K, Wagner D, Schmidt I, Meinlschmidt G, Hellhammer DH, Heim C (2007) The low-dose dexamethasone suppression test in fibromyalgia. J Psychosom Res 62:85-91.
Abstract: OBJECTIVE: Fibromyalgia syndrome (FMS) has been associated with decreased cortisol secretion. Patients with posttraumatic stress disorder (PTSD) exhibit similar hypocortisolism in the context of increased negative feedback sensitivity of the hypothalamic-pituitary-adrenal (HPA) axis. Because trauma and PTSD have been associated with fibromyalgia, we evaluated whether patients with fibromyalgia demonstrate increased HPA feedback sensitivity. METHOD: Baseline blood samples were obtained at 0800 h, and 0.5 mg of dexamethasone was administered to 15 female patients with FMS and 20 normal controls at 2300 h. Adrenocorticotropin (ACTH), cortisol, and dexamethasone levels were measured at 0800 h after dexamethasone intake. RESULTS: There were no group differences in mean ACTH or cortisol levels or in ACTH/cortisol ratio at baseline. After dexamethasone intake, patients with FMS exhibited more pronounced suppression of cortisol but not of ACTH, as well as increased ACTH/cortisol ratios compared with controls. Percent cortisol suppression was associated with pain and fatigue, while ACTH/cortisol ratio and dexamethasone availability were associated with stress and anxiety measures. CONCLUSION: Our results suggest increased sensitivity to glucocorticoid feedback, manifested at the adrenal level, in FMS

Wise SS, Thompson WD, Aboueissa AM, Mason MD, Wise JP, Sr. (2007) Particulate depleted uranium is cytotoxic and clastogenic to human lung cells. Chem Res Toxicol 20:815-820.
Abstract: Depleted uranium (DU) is commonly used in military armor and munitions, and thus, exposure of soldiers and non-combatants is potentially frequent and widespread. DU is considered a suspected human carcinogen, affecting the bronchial cells of the lung. However, few investigations have studied DU in human bronchial cells. Accordingly, we determined the cytotoxicity and clastogenicity of both particulate (water-insoluble) and soluble DU in human bronchial fibroblasts (WTHBF-6 cells). We used uranium trioxide (UO_3) and uranyl acetate (UA) as prototypical particulate and soluble DU salts, respectively. After a 24 h exposure, both UO_3 and UA induced concentration-dependent cytotoxicity in WTHBF-6 cells. Specifically, 0.1, 0.5, 1, and 5 µg/cm^2 UO_3 induced 99, 57, 32, and 1% relative survival, respectively. Similarly, 100, 200, 400, and 800 µM UA induced 98, 92, 70, and 56% relative survival, respectively. When treated with chronic exposure, up to 72 h, of either UO_3 or UA, there was an increased degree of cytotoxicity. We assessed the clastogenicity of these compounds and found that at concentrations of 0, 0.5, 1, and 5 µg/cm2 UO3, 5, 6, 10, and 15% of metaphase cells exhibit some form of chromosome damage. UA did not induce chromosome damage above background levels. There were slight increases in chromosome damage induced when we extended the UO3 treatment time to 48 or 72 h, but no meaningful increase in chromosome damage was observed with chronic exposure to UA

Wood PB, Schweinhardt P, Jaeger E, Dagher A, Hakyemez H, Rabiner EA, Bushnell MC, Chizh BA (2007) Fibromyalgia patients show an abnormal dopamine response to pain. Eur J Neurosci 25:3576-3582.
Abstract: Fibromyalgia is characterized by chronic widespread pain and bodily tenderness and is often accompanied by affective disturbances. Accumulating evidence indicates that fibromyalgia may involve a dysfunction of modulatory systems in the brain. While brain dopamine is best known for its role in pleasure, motivation and motor control, recent evidence suggests that it is also involved in pain modulation. Because dopamine is implicated in both pain modulation and affective processing, we hypothesized that fibromyalgia may involve a disturbance of dopaminergic neurotransmission. Fibromyalgia patients and matched healthy control subjects were subjected to deep muscle pain produced by injection of hypertonic saline into the anterior tibialis muscle. In order to determine the endogenous release of dopamine in response to painful stimulation, we used positron emission tomography to examine binding of [(11)C]-raclopride (D2/D3 ligand) in the brain during injection of painful hypertonic saline and nonpainful normal saline. Fibromyalgia patients experienced the hypertonic saline as more painful than healthy control subjects. Control subjects released dopamine in the basal ganglia during the painful stimulation, whereas fibromyalgia patients did not. In control subjects, the amount of dopamine release correlated with the amount of perceived pain but in fibromyalgia patients no such correlation was observed. These findings provide the first direct evidence that fibromyalgia patients have an abnormal dopamine response to pain. The disrupted dopaminergic reactivity in fibromyalgia patients could be a critical factor underlying the widespread pain and discomfort in fibromyalgia and suggests that the therapeutic effects of dopaminergic treatments for this intractable disorder should be explored

Yamasue H, Abe O, Kasai K, Suga M, Iwanami A, Yamada H, Tochigi M, Ohtani T, Rogers MA, Sasaki T, Aoki S, Kato T, Kato N (2007) Human brain structural change related to acute single exposure to sarin. Ann Neurol 61:37-46.
Abstract: OBJECTIVE: This study aimed to identify persistent morphological changes subsequent to an acute single-time exposure to sarin, a highly poisonous organophosphate, and the neurobiological basis of long-lasting somatic and cognitive symptoms in victims exposed to sarin. METHODS: Thirty-eight victims of the 1995 Tokyo subway sarin attack, all of whom had been treated in an emergency department for sarin intoxication, and 76 matched healthy control subjects underwent T1-weighted and diffusion tensor magnetic resonance imaging (DTI) in 2000 to 2001. Serum cholinesterase (ChE) levels measured immediately and longitudinally after the exposure and the current severity of chronic reports in the victims were also evaluated. RESULTS: The voxel-based morphometry exhibited smaller than normal regional brain volumes in the insular cortex and neighboring white matter, as well as in the hippocampus in the victims. The reduced regional white matter volume correlated with decreased serum cholinesterase levels and with the severity of chronic somatic complaints related to interoceptive awareness. Voxel-based analysis of diffusion tensor magnetic resonance imaging further demonstrated an extensively lower than normal fractional anisotropy in the victims. All these findings were statistically significant (corrected $p < 0.05$). INTERPRETATION: Sarin intoxication might be associated with structural changes in specific regions of the human brain, including those surrounding the insular cortex, which might be related to elevated subjective awareness of internal bodily status in exposed individuals

Yoshiuchi K, Cook DB, Ohashi K, Kumano H, Kuboki T, Yamamoto Y, Natelson BH (2007) A real-time assessment of the effect of exercise in chronic fatigue syndrome. Physiol Behav 92:963-968.
Abstract: Patients with chronic fatigue syndrome (CFS) report substantial symptom worsening after exercise. However, the time course over which this develops has not been explored. Therefore, the objective of this study was to investigate the influence of exercise on subjective symptoms and on cognitive function in CFS patients in natural settings using a computerized ecological momentary assessment method, which allowed us to track the effects of exercise within and across days. Subjects were 9 female patients with CFS and 9 healthy women. A watch-type computer was used to collect real-time data on physical and psychological symptoms and cognitive function for 1week before and 2weeks after a maximal exercise test. For each variable, we investigated temporal changes after exercise using multilevel modeling. Following exercise, physical symptoms did get worse but not until a five-day delay in CFS patients. Despite this, there was no difference in the temporal pattern of changes in psychological symptoms or in cognitive function after exercise between CFS patients and controls. In conclusion, physical symptoms worsened after several days delay in patients with CFS following exercise while psychological symptoms or cognitive function did not change after exercise

Zimmerman KL, Barber DS, Ehrich MF, Tobias L, Hancock S, Hinckley J, Binder EM, Jortner BS (2007) Temporal clinical chemistry and microscopic renal effects following acute uranyl acetate exposure. Toxicol Pathol 35:1000-1009.
Abstract: Military use of depleted uranium (DU) has renewed interest in the toxicology of this metal. In this study, the nephrotoxicity of single exposure DU was assessed with and without pre-exposure stress. Adult male Sprague-Dawley rats (n = 288) were administered a single IM dose of 0, 0.1, 0.3 or 1.0 mg/kg DU. Corticosterone concentrations (ng/ml, mean +/- SD) were 763.65 +/- 130.94 and 189.80 +/- 90.81 for swim stressed and unstressed rats. Serum and kidney uranium concentration, hematocrit, chemistry, and renal histology were assessed on sacrifice days 1, 3, 7 and 30 post-DU-dosing. Dose related increases in serum and kidney uranium were noted. DU concentration peaked day 1 in the kidney and days 3-7, in the serum. Dose-related elevations of Cr and BUN concentrations were seen on days 3 and 7. A decline in serum albumin coincided with Cr and BUN suggesting protein losing nephropathy. Dose related acute tubular necrosis and proliferative glomulonephritis were seen. Tubular regeneration in low dose rats was almost complete by day 30. High dose rats had extensive tubular necrosis and delayed regeneration with focal residual chronic interstitial nephritis and cortical scarring. Glomular changes were reversed in all treatment groups by day 30. Stress exposure had no impact on any measured renal parameter

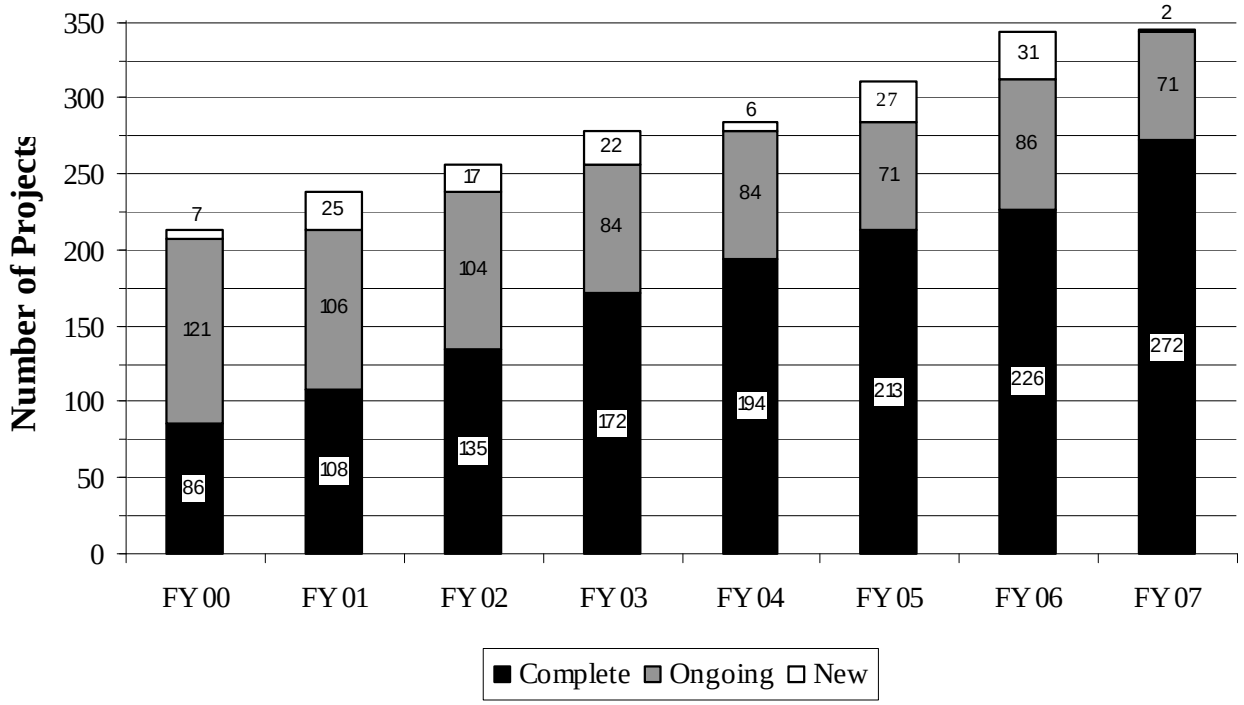
IV. RESEARCH FUNDING TRENDS

The following section provides a quantitative overview of the current research portfolio on GWVI and the evolution of the portfolio since 1998. Topics that are covered include research expenditures by VA, DoD, and HHS from FY 1998-2007, and the number of research projects in which the Federal Government has invested.

VA, DoD, and HHS sponsored a total of 345 distinct research projects on GWVI during the period of FY 1992 through FY 2007. 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 2007 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, 2007, 272 projects (79 percent of the 345 projects) were completed, and 73 projects (21 percent) were new or ongoing; the numbers of new and ongoing projects are shown in Figure IV-1.

Figure IV-1. Cumulative Number of Funded Projects (FY 2000 – FY2007)



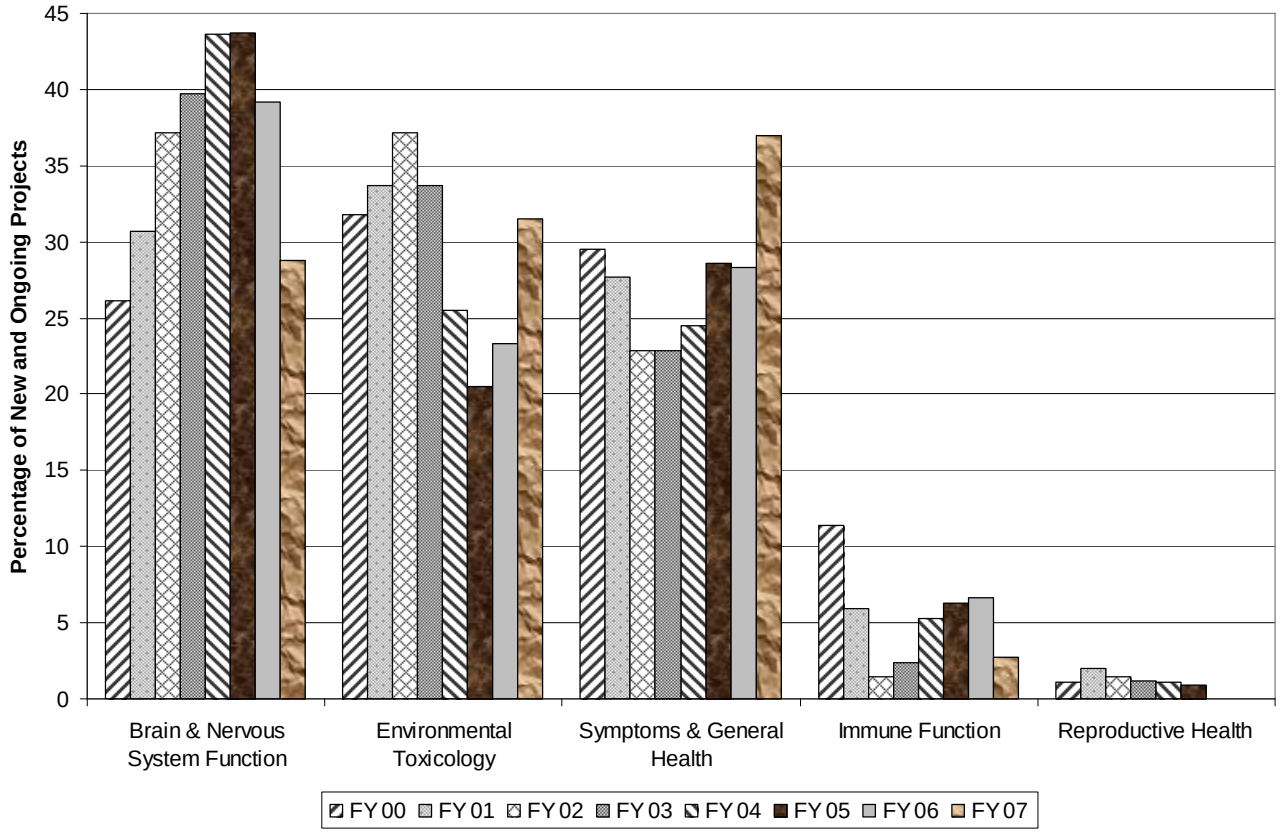
The appropriated funds for FY 1998 through 2007, centrally obligated to each project, are shown in Appendix C and summarized in Table IV-1. Federal funding for GW research totaled $267 million during this period. Funds obligated for these projects prior to FY 1998 are not shown in either Table IV-1 or 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*.

Table IV-1. 10-Year (FY 1998-2007) Funding Trends for GW Research in Millions of Dollars

Department	FY '98	FY '99	FY '00	FY '01	FY '02	FY '03	FY '04	FY '05	FY '06	FY '07	Total Costs FY '97-'07
DoD	$ 13.2	$ 22.7	$ 23.9	$ 31.6	$ 18.8	$ 16.4	$ 10.8	$ 10.1	$ 10.1	$ 3.4	**$ 161.0**
HHS	$ 1.6	$ 1.6	$ 1.6	$ 1.0	$ 0.8	$ 1.0	$ 0.5	$ 0.5	$ 0.4	$ 0.4	**$ 9.4**
VA	$ 4.7	$ 9.0	$12.0	$ 8.6	$ 4.5	$ 5.8	$ 7.6	$ 9.5	$12.9	$ 22.0	**$ 96.6**
Total	**$ 19.5**	**$ 33.3**	**$ 37.5**	**$ 41.2**	**$ 24.1**	**$ 23.2**	**$ 18.9**	**$ 20.1**	**$ 23.4**	**$ 25.8**	**$ 267.0**

The annual distribution of new and ongoing projects within the five major Research Focus Areas is shown in Figure IV-2. From FY 2000 through 2007 new and ongoing research assigned to Brain and Nervous System Function, Environmental Toxicology and General Health and Symptoms has represented 92.9 ± 1.2 percent of the new and ongoing projects.

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



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). The two key priority areas for the FY06 GWVIRP were "Identification and evaluation of currently available treatments" and "Identification of objective indicators of pathology that distinguish ill from healthy veterans." Proposals were reviewed and funding decisions made during FY07 (see New Projects below).

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. Due to the timing of the contract, project funding is lagging one year behind (i.e., projects that start in FY 2007 are funded from the FY 2006 VA research appropriation). Because funds were released for these projects in FY07, they are counted as new projects in Appendix C

B. Portfolio Review

Currently funded projects in infectious diseases will be considered to be closed as of FY 2006 (i.e., no FY 2007 funds listed in Appendix C). These projects and their prior funding will remain in Appendices A, B, and C to retain continuity with previous *Annual Reports to Congress*.

Similarly, PTSD-related projects that were previously included in the Federal Gulf War research portfolio will be closed as of FY2007 if they do not directly study populations of ill Gulf War veterans or do not investigate new treatments that may prove beneficial for ill Gulf War veterans.

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 funded using funds appropriated in prior years or 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)

Three projects were funded through the FY06 Peer Reviewed Medical Research Program (PRMRP) managed by the Congressionally Directed Medical Research Program (CDMRP) at DoD. These projects focused on Environmental Toxicology (1) and Symptoms and General Health (2).

*DoD-167, "Mass Spectrometry to Identify New Biomarkers of Nerve Agent Exposure" will use Mass Spectrometry to first identify proteins in human serum that covalently bind soman, a chemical warfare agent classified as a nerve agent, and then will determine the effect of soman binding on function (e.g., enzymatic) of these protein. This research will identify new biomarkers of soman exposure and then identify which of these biomarkers could act as bioscavengers of soman. The latter could be subsequent used in the design of pretreatment strategies to limit nerve agent toxicity.

*DoD-168, "Developing Biomarkers for Fibromyalgia " will explore the pathogenesis of fibromyalgia as seen in aberrant central neural function within pain processing regions of the brain using different in situ neuroimaging modalities. This study will potentially identify biomarkers for the firm diagnosis of and successful treatment for fibromyalgia.

*DoD-169, "Development of Novel Therapy for Chronic Neuropathic Pain" will identify small molecules that selectively inhibit synaptic functions of N-type Ca2+ channels in dorsal root ganglia, which is a well-validated component of the chronic pain pathway. This study could provide a class of pain relief agents that can be used to treat opiate-resistance chronic pain.

Nine projects were funded through the FY06 Gulf War Veterans' Illnesses Research Program (GWVIRP) managed by the Congressionally Directed Medical Research Program (CDMRP) at DoD. These projects focused on Brain and Nervous System Function (2), Environmental Toxicology (2), and Symptoms and General Health (5).

*DoD-170, "Structural MRI and Cognitive Correlates in Pest-Control Personnel from Gulf War I" will potentially elucidate objective biomarkers of ill-GW1 veterans, who were pesticide (i.e., organophosphates) applicators. This will be accomplished through correlating their exposures to organophosphates to changes in brain morphometrics (e.g., cortical and subcortical brain white matter volume) measured by structural magnetic resonance imaging and changes in measures of cognitive function. The results should contribute to better diagnosis and treatment of military personnel, including GW veterans, exposed to organophosphates.

*DoD-171, "Q10 for Gulf War Veterans" is a randomized, placebo-controlled, double-blind cross-over study designed to determine if coenzyme Q10, a physiological cofactor critical to mitochondrial ATP synthesis, will alter subjective evaluation of health, fatigue, muscle pain, muscle strength and other symptoms in a group of GW veterans showing criteria for GW illness.

*DoD-172, "CNDP1 Polymorphisms and Carnosine Therapy in GWI" will explore the relationship between the symptoms of veterans of the GW with different alleles for the enzyme carnosine dipeptidase. The study of this relationship will include identifying the effects of oral carnosine, a substrate of this enzyme, in a placebo-controlled, double-blinded clinical trial on measures of pain, fatigue and neuromuscular function. Additional in vitro studies are planned to determine the mechanism of the about relationship.

*DoD-173, "A Randomized, Double-Blind, Placebo-Controlled, Crossover Trial of Mifepristone in Gulf War Veterans with Chronic Multisymptom Illness" will determine whether mifepristone, a glucocorticoid receptor antagonist, can reduce the neuroendocrine alterations that have been described in GW veterans. The effects of mifepristone on physical health, cognitive function, the hypothalamic-pituitary-adrenal axis, and symptoms characteristic of or associated with chronic multi-symptom illness will be determined in a randomized double-blind placebo trial of mifepristone in GW veterans.

*DoD-174, "Autonomic Biomarkers and Treatment for Gulf War Illness" will use a mouse model, generated by low-dose sarin exposure, to discover the mechanisms of and treatments for the central neural pathologies that have been associated with GW illness.

*DoD-175, "Novel Pharmacological Approaches for Treatment of Neurotoxicity Induced by Chronic Exposure to Depleted Uranium" will study the therapeutic effectiveness of specific agents to reduce the neurotoxicity generated in rats by implanted depleted uranium.

*DoD-176, "Studies on Axonal Transport in an Animal Model for Gulf War Syndrome" will use a recently established animal model for amyotrophic lateral sclerosis (ALS), which is twice as likely to occur in GW veterans than the general population, to determine if the nerve degeneration underlying ALS may be caused by chemicals that veterans of the GW may have been exposed to while in theater.

*DoD-177, "Randomized Trial of an Environmental Medicine Approach to Gulf War Veterans' Illness" will determine in veterans with GW illness if a controlled environment (i.e., living in a environmentally controlled room with relatively clean air, eating organically grown foods free of chemical contaminants, drinking filtered spring water free of environmental pollutants, provocative-neutralization testing, vitamin and nutrient supplementation and sauna-detoxification) will lessen scores on tests associated with GW illness.

*DoD-178, "Analysis of Paraoxonase Status among US Navy Gulf War Veterans with Increased Postwar Symptoms, Psychological Morbidity and Medical Conditions" will gain a better understanding of the relationship between post-GW symptoms in US Navy Construction Batalion personnel to their deployment-related exposures to organophosphate pesticides, to their use of pyridostigmine bromide tablets and to their individual paraoxonase activity.

Department of Veterans Affairs (VA)

VA initiated funding for 2 new projects during FY 2007; one focused on Environmental Toxicology and the other on Symptoms and General Health.

VA-149, "Behavior of Neural Stem Cells in a Rat Model of GWS" will determine if neuron production in the hippocampus and if measures of learning and memory functions in rats are impaired because of prolonged exposure to a combination of agents (i.e., pyridostigmine bromide, DEET, permethrin, and physiological stress). Furthermore, if changes are seen in these functions, then the study will explore treatment strategies to reverse these changes. This study will determine some possible mechanisms and treatments for a set of non-specific central nervous system symptoms associated with Gulf War veterans' illnesses.

VA-150, "Gulf War Veterans Illnesses' Research IDIQ Contract" supports support a contractual agreement with the University of Texas Southwestern Medical Center for research related to illnesses affecting Gulf War veterans. Activities covered by this contract in FY 2007 included:

1. Purchase of additional imaging equipment
2. Establishment an administrative management core (includes UTSW Merit Review Group which will direct the scope and direction of the program, as well as approve projects for submission as task orders)
3. New Telephone Survey of Ill Gulf War Veterans and establishment of a serum DNA Bank
4. Establishment of PON (Paraoxonase) Lab for genomics
5. Establishment of Neuroimaging Cores

VI. REFERENCES

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Appendices

Federally Funded Research Projects

Appendix A

Project Index By Department

DEPARTMENT OF DEFENSE PROJECTS

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

DoD-013	Effects of Persian Gulf War Service on Military Working Dogs
DoD-014	Risk Factors Among US Army Soldiers for Enrolling on the Department of Veterans Affairs Gulf War Registry
DoD-015	Comparative Mortality Among US Military Personnel Worldwide During Operations Desert Shield and Desert Storm
DoD-016	Kuwait Oil Fire Health Risk Assessment
DoD-017	Retrospective Studies Involving Military Use of Pyridostigmine as a Pretreatment for Nerve Agent Poisoning
DoD-018	Kuwait Oil Fires Troop Exposure Assessment Model (TEAM)
DoD-019	Persian Gulf Veterans Health Tracking System
DoD-021	Study of Variability In Pyridostigmine Inhibition of Blood Cholinesterases in Healthy Adults and Individuals With Symptoms Following Participation in Operation Desert Storm
DoD-022	Chronic Organophosphorus Exposure and Cognition
DoD-023	Acute and Long-Term Impact of Deployment to Southwest Asia on the Physical and Mental Health of Soldiers and their Families
DoD-030	Epidemiological Studies Persian Gulf War Illnesses, PG Women's Health Linkage Study
DoD-031	Dysregulation of the Stress Response in the Persian Gulf Syndrome
DoD-032	Neuropsychological Functioning in Persian Gulf Era Veterans
DoD-033	Effects of Pyridostigmine in Flinders Line Rats Differing in Cholinergic Sensitivity
DoD-034	Characterization of Emissions from Heaters Burning Leaded Diesel Fuel in Unvented Tents
DoD-035	Feasibility of Investigating Whether There is a Relationship Between Birth Defects and Service in the Gulf War
DoD-036	Fatigue in Persian Gulf Syndrome-Physiologic Mechanisms
DoD-037	Neurobehavioral and Immunological Toxicity of Pyridostigmine, Permethrin, and DEET in Male and Female Rats
DoD-038	Diagnostic Antigens of Leishmania tropica
DoD-039	A Controlled Epidemiological and Clinical Study into the Effect of Gulf War Service on Servicemen and Women of the United Kingdom Armed Forces
DoD-040	Psychological and Neurobiological Consequences of the Gulf War Experience

DoD-041	Evaluation of Muscle Function in Persian Gulf Veterans
DoD-042	The Symptomatic Persian Gulf Veterans Protocol: An Analysis of Risk Factors with an Immunologic and Neuropsychiatric Assessment
DoD-044	Investigation of Seminal Plasma Hypersensitivity Reactions
DoD-045	Air Force Women's Health Surveillance Study
DoD-046	Exploratory Data Analysis with the CCEP Database
DoD-047	Study of Mycoplasmal Infections in Gulf War Veterans
DoD-048	Assessment of Genomic Instability via Chromosome 7 Inversion Frequency in a Gulf-War Syndrome Cohort vs Selected Control Groups
DoD-049	Diagnosis and Dosimetry of Exposure to Sulfur Mustard: Development of Standard Operating Procedures and Exploratory Research on Protein Adducts
DoD-050	Toxicokinetics of 0-Ethyl S-(2-Diisopropylaminoethyl) Methylphosphonothioate [(+)-VX] in Rats, Hairless Guinea Pigs and Marmosets - Identification of Metabolic Pathways
DoD-051	Transgenic Engineering of Cholinesterases: Tools for Exploring Cholinergic Responses
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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
DoD-061	Neurophysiologic and Neuropathologic Effects in Monkeys of Low Level Exposures to Sarin, Pyridostigmine, Pesticides, and Botulinum Toxoid
DoD-062	Sarin and Pyridostigmine Interaction under Physical Stress: Neurotoxic Effects in Mice

DoD-063	PGW Veterans: Epidemiological and Clinical Evidence for Residual Organophosphate Neurotoxicity
DoD-064	Individual Differences in Neurobehavioral Effects of Pyridostigmine
DoD-065	Multi-disciplinary Pathophysiologic Studies of Neurotoxic Gulf War Related Syndromes Leading to Diagnosis and Treatment
DoD-066	Testing for mycoplasmal infection replicability of nucleoprotein gene tracking and forensic polymerase chain reaction
DoD-067	Antibacterial Treatment Method Based Upon the Excretion of Dead and Decaying Spherical Bacteria
DoD-069	Five-Year Follow-Up of Army Personnel Exposed to Chemical Warfare Agents
DoD-070	War Syndromes from 1900 to the Present: Symptom Patterns and Long-term Health Outcomes
DoD-071	A Comparison of Post Deployment Hospitalization Between Vietnam and Gulf War Veterans
DoD-072	Long-term Effects of Subchronic Exposure to Sarin, Alone and with Stress or Other Chemicals
DoD-073	Post-deployment Morbid Stress, Behavior and Health: Developing a Model for Predicting Morbidity, Mortality, and other Adverse Outcomes
DoD-074	Relationship of Stress Exposures to Health in Gulf War Veterans
DoD-075	Toxic Interactions of Prophylactic Drugs and Pesticides
DoD-076	Evaluations of Immunotoxicity due to Concurrent Exposure to DEET, Pyridostigmine, and JP-8 Jet Fuel
DoD-077	Percutaneous Absorption of Chemical Mixtures Relevant to the Gulf War
DoD-078	Experimental Models of Gulf War Syndrome
DoD-079	Time Course of Stress-induced Impairment of Blood Brain Barrier
DoD-080	Molecular Regulation of Corticosteroid Receptor Expression in Stress-Responsive Cells
DoD-081	Immunotoxicity due to Coexposure to DEET, Pyridostigmine, and Stress
DoD-082	Feasibility of Developing a Registry of PTSD Affected Veteran Sib Pairs
DoD-083	Risk for Stress-related Substance Abuse: the Effects of Family History of Alcoholism
DoD-084	Psychobiologic Alterations in Persian Gulf War Veterans with and without PTSD
DoD-085	CNS Cytokines and CRH in Gulf War Veterans with Multiple Unexplained Symptoms
DoD-086	Effects of Combat Stress on Structure and Function of the Hippocampus

DoD-087	Measurement and Validation of Psychosocial Risk and Resilience Factors Accounting for Physical and Mental Health and Health-Related Quality of Life among PGWVs
DoD-088	Clinical Relevance of Novel Immunological Markers in PTSD
DoD-089	Limbic Blood Flow and Opiate Receptor PET in Posttraumatic Stress Disorder
DoD-090	SPECT Benzodiazepine Receptor and MR Imaging in PTSD
DoD-091	Neurological and Circadian Substrates of PTSD-like Behaviors
DoD-092	Traumatic Experiences Persistently Enhance Cue-dependent Learning: Toward an Animal Model of Chronic Stress and Posttraumatic Stress Disorder
DoD-093	Troops Exposed to Nerve Agents at Aberdeen Proving Ground: Follow-Up
DoD-094	Combined Analysis of the VA and DoD Gulf War Clinical Registries: A Study of Clinical Findings from Systematic Medical Examinations of 100,000 U.S. Gulf War Veterans
DoD-095	Development of Diagnostic tools and alternative treatment drugs for Leishmania
DoD-096	Deployment Health Center
DoD-097	Surveillance of B. pertussis among Military Trainees with Respiratory Disease: Development and Validation of a Highly Sensitive PCR and Beacon Probe based Method for Diagnosis of Pertussis
DoD-098	Investigation of a Baseline Medical Database to Evaluate the Health of Military Forces and Veterans
DoD-099	DoD-wide Medical Surveillance for Potential Long-Term Adverse Events associated with Anthrax Immunization in Active Duty Service Members, Proposal 1: Hospitalizations
DoD-100	Antibodies to Squalene
DoD-101	Mechanisms in Chronic Multisymptom Illnesses
DoD-102	Case-Control Study of Fatal Motor Vehicle Crashes Among Gulf War and Non-Deployed Veterans
DoD-103	Human Metabolism and Interactions of Deployment-related Chemicals
DoD-104	Clinical Evaluation of a Proposed New Gulf War Syndrome
DoD-105	Neuroplasticity and Calcium Signaling in Stressed Rat Amygdala
DoD-106	The Role of Th1/Th2 cytokine balance in Gulf War-related illness
DoD-107	Stress, Organophosphates and Blood Brain Barrier Integrity
DoD-108	Health Status of Current National Guard Members

DoD-109	Disordered Responses to Orthostatic Stress in the Pathogenesis of Gulf War Syndrome Symptoms
DoD-110	Predictors of Career and Family Dysfunction in Young Adults Enlisting in the United States Navy
DoD-111	Autonomic Dysfunction in Gulf War Veterans
DoD-112	Role of Respirable Saudi Arabian Sand and Pyridostigmine in the Gulf War Syndrome: An Autoimmune Adjuvant Disease?
DoD-113	Interactions of Subsymptomatic Doses of Sarin with Pyridostigmine: Neurochemical, Behavioral, and Physiological Effects
DoD-114	A Re-examination of Neuropsychological Functioning in Persian Gulf War Veterans
DoD-115	A Randomized, Multi-Center, Controlled Trial of Multi-Model Therapy in Veterans with Gulf War Illnesses (EBT) (See also VA-62; formerly VA/DoD 1D)
DoD-116	VA/DoD Core Funding of the Medical Follow-Up Agency (See also VA-63; formerly VA-DoD-2D/2V)
DoD-116A	Follow-Up Investigation of Troops Exposed to Nerve Agents at Aberdeen Proving Ground (Pilot Study) (See also VA-63A; formerly VA/DoD-2DA)
DoD-116B	Patterns of Pre-Persian Gulf War Illness and Health Care Seeking, Pilot Study (See also VA-63B; formerly VA/DoD- 2DB)
DoD-117	Patterns of Pre-Persian Gulf War Illness and Health Care Seeking
DoD-118	An Epidemiological Investigation into the Occurrence of Amyotrophic Lateral Sclerosis (ALS) Among Gulf War Veterans (See also VA-61)
DoD-119	Antibiotic Treatment of Gulf War Veterans' Illnesses (ABT) (See also VA-55)
DoD-120	Assessing the Potential Health Impact of the Gulf War on Saudi Arabia National Guard Members and Their Dependents
DoD-121	Evaluation of the Health Risks of Embedded Depleted Uranium Shrapnel During Pregnancy and Offspring Development
DoD-122	Carcinogenic Potential of Depleted Uranium and Tungsten Alloys
DoD-123	Immunotoxicity of Depleted Uranium and Heavy Metal Tungsten Alloys
DoD-124	Randomized, Controlled Trial for Combination Treatment with Pyridostigmine, DEET, and Permethrin
DoD-125	A Randomized Clinical Trial of Cognitive-Behavioral Treatment for PTSD in Women (See VA-74)
DoD-126	Blood-Brain Barrier Transport of Uranium
DoD-127	Depleted Uranium Fragment Carcinogenicity: Extrapolation of Findings in Rodents to Man

DoD-128	Multifactorial Assessment of Depleted Uranium Neurotoxicity
DoD-129	Inhalation of Uranium Oxide Aerosol: CNS Deposition, Neurotoxicity, and Role in Gulf War Illness
DoD-130	Carcinogenicity and Immunotoxicity of Embedded Depleted Uranium and Heavy-Metal Tungsten Alloys in Rodents
DoD-131	Magnetic Resonance and Spectroscopy of the Human Brain in Gulf War Illnesses
DoD-132	Impaired Auditory Sensory Gating, Acoustic Startle Response: Effects of Long and Short Deployments on Army Combat Readiness
DoD-133	Odors, Deployment Stress, and Health: A Conditioning Analysis of Gulf War Syndrome
DoD-134	Identification and Development of Biological Markers of Human Exposure to the Insecticide Permethrin
DoD-135	Biochemical Markers for Exposure to Low Doses of Organophosphorous Exposure
DoD-136	A Mechanism-Based, Molecular Fingerprint Strategy for Detecting Biomarkers of Organophosphate Exposure
DoD-137	Low Level Exposure to Sulfur Mustard: Development of a SOP for Analysis of Albumin Adducts and of a System for Non-Invasive Diagnosis on Skin
DoD-138	Improving Blood Monitoring of Enzymes as Biomarkers of Risk from Anticholinergic Pesticides and Chemical Warfare Agents
DoD-139	Assessment of the Role of Stress-Activated Kinase in the Pathogenesis of Gulf War Illnesses
DoD-140	US Department of Defense Surveillance for Neoplasms in Infancy
DoD-141	Physical, Mental, Social, and Family Health Outcomes of Gulf War Veterans
DoD-142	Illnesses Among Persian Gulf War Veterans: Case Validation Studies (Iowa / Great Britain)
DoD-143	Millennium Cohort Study (See also VA-78)
DoD-144	Psychological Health Screening: Methods and Metrics for Deployed Forces
DoD-145	Early Intervention Research Program to Enhance Soldier Resilience
DoD-146	Assessment of Toxicology Assays Methods & Chemical Exposures Among a Cohort of US Marines
DoD-147	Development and Validation of the Automated Neuropsychological Assessment Metric (ANAM) for Deployment Health Monitoring Applications
DoD-148	Predicting operational readiness for deployed Army National Guard and Army Reserve soldiers and families

DoD-149	Longitudinal Health Study of Gulf War Veterans
DoD-150	Validation Study of Gulf War Deployment Files
DoD-151	Mechanisms and Consequences of Vaccine Effects on Th1/Th2 Balance in Gulf War Veterans
DoD-152	Characterization of Intracellular Signaling Pathways Activated by Nerve Agents
DoD-153	Gulf War Illness Research
DoD-154	Prospective Assessment of Neurocognition in Future Gulf-deployed and Gulf-nondeployed Military Personnel: A Pilot Study (See also VA-88)
DoD-155	Neuropsychological Functioning in Gulf War Veterans Exposed to Pesticides and Pyridostigmine Bromide
DoD-156	The Effects of Diesel Exhaust and Stress on the Acute Phase Response and Symptoms in the Chemically Intolerant
DoD-157	Novel Leishmania and Malaria Potassium Channels: Candidate Therapeutic Targets
DoD-158	Preconceptional Paternal Exposure to Embedded Depleted Uranium Fragments: Transmission of Genetic Damage To Offspring
DoD-159	Neurotoxicity from Chronic Exposure to Depleted Uranium
DoD-160	Characterization of the Reproductive Toxicity of Depleted Uranium
DoD-161	Glutamate Receptor Aptamers and ALS
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
DoD-167	Mass Spectrometry to Identify New Biomarkers of Nerve Agent Exposure
DoD-168	Developing Biomarkers for Fibromyalgia
DoD-169	Development of Novel Therapy for Chronic Neuropathic Pain
DoD-170	Structural MRI and Cognitive Correlates in Pest-Control Personnel from Gulf War I

DoD-171	Q10 for Gulf War Veterans
DoD-172	CNDP1 Polymorphisms and Carnosine Therapy in GWI
DoD-173	A Randomized, Double-Blind, Placebo-Controlled, Crossover Trial of Mifepristone in Gulf War Veterans with Chronic Multisymptom Illness
DoD-174	Autonomic Biomarkers and Treatment for Gulf War Illness
DoD-175	Novel Pharmacological Approaches for Treatment of Neurotoxicity Induced by Chronic Exposure to Depleted Uranium
DoD-176	Studies on Axonal Transport in an Animal Model for Gulf War Syndrome
DoD-177	Randomized Trial of an Environmental Medicine Approach to Gulf War Veterans' Illness
DoD-178	Analysis of Paraoxonase Status among US Navy Gulf War Veterans with Increased Postwar Symptoms, Psychological Morbidity and Medical Conditions

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
HHS-004	Suspected Increase of Birth Defects and Health Problems Among Children Born to Persian Gulf War Veterans In Mississippi
HHS-005	Cognitive Function and Symptom Patterns in Persian Gulf Veterans
HHS-006	Defining Gulf War Illness
HHS-007	Immunotoxicity of Dermal Permethrin and Cis-Urocanic Acid
HHS-008	Strategy to Identify Non-Additive Response to Chemical Mixtures
HHS-009	Improving Health Risk Communications to Prevent Unexplained Illnesses Related to Military Deployments
HHS-010	Health-e Voice: Optimized Implementation of a Stepped Clinical Risk Communications Guideline
HHS-011	Deployment to the Gulf War and the Subsequent Development of Cancer
HHS-012	Genetic Epidemiology of ALS in Veterans

DEPARTMENT OF VETERANS AFFAIRS PROJECTS

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

VA-006E	Clinical and Epidemiology Leishmania Research
VA-007	Desert Storm Reunion Survey
VA-008	Psychological Test Data of Gulf War Veterans Over Time
VA-009	Evaluation of Cognitive Functioning in Persian Gulf War Veterans Reporting War-related Health Problems
VA-010	Memory and Attention in PTSD
VA-011	Neuropsychological Functioning in Veterans
VA-012	Psychological Assessment of Operation Desert Storm Returnees
VA-013	Neurobehavioral Aspects of Persian Gulf Experiences: A Pilot Study
VA-015	Vaccine-Mediated Immunity Against Leishmaniasis
VA-016	Protective Immunity in Experimental Visceral Leishmaniasis
VA-017	Immunological Evaluation of Persian Gulf Veterans
VA-018	Chronic Gastrointestinal Illness in Persian Gulf Veterans
VA-020	Psychological Adjustment in Operation Desert Shield/Storm Veterans
VA-021	A Comparison of PTSD Symptomatology among Three Army Medical Units Involved in ODS
VA-036	Stress Symptoms and Their Causal Attribution in Desert Storm Veterans
VA-040	Musculoskeletal Symptoms in Gulf War Syndrome
VA-046	Diarrhea in Persian Gulf Veterans: An Irritable Bowel-Like Disorder
VA-047	Retrospective Verification of Mustard Gas Exposure
VA-048	Cross-Sensitization as a CNS Model for Gulf War Chemical Intolerance
VA-049	Sensitivity to Pyridostigmine Bromide: Persistent Neural Dysfunction
VA-050	Neuropsychological findings in a sample of Operation Desert Storm veterans
VA-051	Psychobiological Assessment of Desert Storm Veterans
VA-053	Spouses and Children Program
VA-054	Follow-up of Psychological and Neurocognitive Gulf War Outcome: Relation to Stress

VA-055	Antibiotic Treatment of Gulf War Veterans' Illnesses (ABT) (See also DoD-119)
VA-056	Birmingham's Gulf War Veterans' Illness Demonstration Clinic (13)
VA-057	Case Management and Residential Rehabilitation for Persian Gulf War Veterans (13)
VA-058	Implementation and Evaluation of Gulf War Veterans' Demonstration Project (13)
VA-059	Demonstration Treatment Program for Gulf War Veterans with Unexplained Physical Symptoms (13)
VA-060	Identification and Management of Sleep Disorders in Gulf War Veterans
VA-061	An Epidemiological Investigation into the Occurrence of Amyotrophic Lateral Sclerosis (ALS) Among Gulf War Veterans (See also DoD-118)
VA-062	A Randomized, Multi-Center, Controlled Trial of Multi-Model Therapy in Veterans with Gulf War Illness (EBT) (See also DoD-115; formerly VA/DoD 1V)
VA-063	VA/DoD Core Funding of the Medical Follow-Up Agency (See also DoD-116; formerly VA/DoD-2V/2D)
VA-063A	Follow-Up Investigation of Troops Exposed to Nerve Agents at Aberdeen Proving Ground(Pilot Study) (See also DoD-116A; formerly VA/DoD-2VA/2DA)
VA-063B	Patterns of Pre-Persian Gulf War Illness and Health Care Seeking Pilot Study (See also DoD-116B; previously VA/DoD-2VB)
VA-064	Boston Environmental Hazards Research Center
VA-064A	Functional Neuroimaging in Lead Exposed Adults
VA-064B	Quantification and Validation of Structure-Function Relationships Through Visuospatial Test Performance
VA-064C	Development of a Structured Neurotoxicant Assessment Checklist (SNAC) for Clinical use in Veteran Populations
VA-065	San Antonio Environmental Hazards Research Center
VA-065A	Does a Variant of the Human SOD2 Gene Increase Sensitivity to Hazards?
VA-065B	The Contribution of FEN-1 to Genetic Integrity Subsequent to Oxidative Stress
VA-065C	The Importance of Hydrogen Peroxide Detoxification in Cellular Protection
VA-065D	Do Defective Gpx1 and ALDH2 Genes Increase Sensitivity to Environmental Hazards?

VA-066	Physiological Responding in Posttraumatic Stress Disorder
VA-067	Olfactory Functioning in Gulf War Veterans
VA-068	Family Study of Fibromyalgia
VA-069	Cardiovascular Hyporeactivity and Fatiguing Illness in Gulf War Veterans
VA-070	A Clinical Evaluation of the Health Status of Persian Gulf War Veterans in VISN 8
VA-071	Central Nervous System Modulation of Visceral Pain in the Persian Gulf Syndrome
VA-072	Roles of Paraoxonase, Butyrylcholinesterase and Stress in Unexplained Illnesses
VA-073	Pain Sensitivity in Gulf War Veterans with Medically Unexplained Musculoskeletal Pain
VA-074	A Randomized Clinical Trial for Cognitive-Behavioral Treatment for PTSD in Women (See DoD-125)
VA-075	ALS and Veterans: Are Veterans at Increased Risk?
VA-076	Analysis of Hippocampal Volume in Aging Combat Veterans with PTSD
VA-077	HPA Axis Reactivity in Men and Women with Chronic PTSD
VA-078	Millennium Cohort Study (See also DoD-143)
VA-080	Neurochemical and Neurobehavioral Impact of Pyridostigmine Bromide Treatment and Stress
VA-081	Stress, Pro-Inflammatory Cytokines and Coping Behavior
VA-082	Pituitary Adrenal Function in People with Fatiguing Illness
VA-083	Neuropsychological Assessment of a Population-Based Sample of Persian Gulf War Veterans and Controls
VA-084	Neurobiology of Severe Psychological Trauma in Women
VA-085	Associative Learning in Veterans with and without Combat Experience
VA-086	A Clinical Trial of Magnetic Stimulation in Depression
VA-087	Improving Outcomes of Depression in Primary Care
VA-088	Prospective Assessment of Neurocognition in Future Gulf-deployed and Gulf-nondeployed Military Personnel: A Pilot Study (See also DoD-154)
VA-089	National Registry of Veterans with Amyotrophic Lateral Sclerosis

VA-090	Differential Gene Expression in Pathologies Associated with Neuronal Hyperexcitability: Links to Gulf War Illness
VA-090A	Neuronal Hyperexcitability and Motor Neuron Regeneration
VA-090B	Gene Expression and Proteomic Strategies in Severe Psychiatric Disorders
VA-090C	Developmental Differences in Alcohol Withdrawal Sensitivity
VA-090D	Seizures and Neuroplasticity: Physiology and Biochemistry
VA-091	The Role of Dietary Choline in Neuroprotection
VA-092	Acetylcholinesterase Activity in Gulf War Veterans
VA-093	HPA Axis Alterations in PTSD: A Comparison of Gulf War and Vietnam Veterans
VA-094	The Immunology of Chronic Cutaneous Leishmaniasis
VA-095	The Role of Signal Regulatory Proteins in Astrocytomas
VA-096	Functional Imaging of Pain in Veterans with Unexplained Muscle Pain
VA-097	Improving a mM-CSF Tumor Vaccine for Established Intracranial Gliomas
VA-098	Post-Transcriptional Gene Regulation of VEGF in Malignant Gliomas
VA-099	Vaccination Against Visceral Leishmaniasis with a Multi-Epitope Vaccine
VA-100	Studies of the Blood-Brain Barrier and it's Manipulation
VA-101	Biomarkers Discovery in ALS
VA-102	Cholinergic and Monoaminergic Influences on Sleep
VA-103	Hypothalamic and Basal Forebrain Regulation of Sleep and Arousal
VA-104	Characterization of Pain Processing Mechanisms in the Irritable Bowel Syndrome
VA-105	Expression of the Major Surface Protease of Leishmania Chagasi
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
VA-113	Novel Cause of Motor Neuron Disease
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
VA-119	Patterns of Microarray Gene Expression in Gulf War Illness
VA-120	Arginase NO Synthase and Cell Death in Amyotrophic Lateral Sclerosis
VA-121	Genes, Environment, and Oxidative Stress in Neurodegenerative Disorders
VA-122	Role of Mitochondrial Oxidative Stress in ALS
VA-123	Interactions Between Maternal Care, Stress and Pyridostigmine Bromide
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
VA-126	Structural Magnetic Resonance Imaging in Gulf War-Era Veterans
VA-127	Interactions of the Leishmania sp. with Mammalian Cells
VA-128	MR Tracking of Stem Cells for Replacement Therapy in ALS
VA-129	Glucocorticoid Responsivity in Gulf War Veterans
VA-130	Tissue Factor and Gulf War-Associated Chronic Coagulopathies
VA-131	Neuroendocrine Regulators and Proteomics in GW Veterans with CMI
VA-132	Immunologic Mechanisms and Biomarkers in Gulf War Illness
VA-133	Longitudinal Study of Gene Expression and Gene Products in Veterans with Gulf War Illness

VA-134	Autonomic Functions of Gulf War Veterans with Unexplained Illnesses
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
VA-138	Inspiratory Flow Dynamics During Sleep in GWS and the Effect of CPAP
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
VA-149	Behavior of Neural Stem Cells in a Rat Model of GWS
VA-150	Gulf War Veterans Illnesses' Research IDIQ Contract

Appendix B

Project List by Research Focus Areas

Brain and Nervous System Function

Clinical

Research Focus	Project Focus	Project	Project Title
	Diagnosis Duty Military - BALSAM	DoD-165	Biomarkers for Amyotrophic Lateral Sclerosis in Active
	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 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	Prevention	DoD-083	Risk for Stress-related Substance Abuse: the Effects of Family History of Alcoholism
Symptoms and General Health	Symptoms	DoD-084	Psychobiologic Alterations in Persian Gulf War Veterans with and without PTSD
Symptoms and General Health	Symptoms	DoD-086	Effects of Combat Stress on Structure and Function of the Hippocampus
Symptoms and General Health	Symptoms	DoD-089	Limbic Blood Flow and Opiate Receptor PET in Posttraumatic Stress Disorder
Symptoms and General Health	Diagnosis	DoD-090	SPECT Benzodiazepine Receptor and MR Imaging in PTSD
Symptoms and General Health	Symptoms	DoD-132	Impaired Auditory Sensory Gating, Acoustic Startle Response: Effects of Long and Short Deployments on Army Combat Readiness
Symptoms and General Health	Diagnosis	DoD-147	Development and Validation of the Automated Neuropsychological Assessment Metric (ANAM) for Deployment Health Monitoring Applications
Symptoms and General Health	Symptoms	HHS-005	Cognitive Function and Symptom Patterns in Persian Gulf Veterans
Symptoms and General Health	Symptoms	VA-004	Boston Environmental Hazards Research Center Program

Brain and Nervous System Function

Clinical

Research Focus	Project Focus	Project	Project Title
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
Symptoms and General Health	Symptoms	VA-021	A Comparison of PTSD Symptomatology among Three Army Medical Units Involved in ODS
Symptoms and General Health	Symptoms	VA-050	Neuropsychological findings in a sample of Operation Desert Storm veterans
Symptoms and General Health	Symptoms	VA-051	Psychobiological Assessment of Desert Storm Veterans
Symptoms and General Health	Symptoms	VA-054	Follow-up of Psychological and Neurocognitive Gulf War Outcome: Relation to Stress
Symptoms and General Health	Symptoms	VA-064	Boston Environmental Hazards Research Center
Symptoms and General Health	Symptoms	VA-066	Physiological Responding in Posttraumatic Stress Disorder
Symptoms and General Health	Symptoms	VA-072	Roles of Paraoxonase, Butyrylcholinesterase and Stress in Unexplained Illnesses
Symptoms and General Health	Symptoms	VA-076	Analysis of Hippocampal Volume in Aging Combat Veterans with PTSD
Symptoms and General Health	Symptoms	VA-077	HPA Axis Reactivity in Men and Women with Chronic PTSD

Brain and Nervous System Function

Clinical

Research Focus	Project Focus	Project	Project Title
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	VA-089	National Registry of Veterans with Amyotrophic Lateral Sclerosis
Symptoms and General Health	Symptoms	VA-093	HPA Axis Alterations in PTSD: A Comparison of Gulf War and Vietnam Veterans
Symptoms and General Health	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	Symptoms; Diagnosis;	DoD-065	Multi-disciplinary Pathophysiologic Studies of Neurotoxic Gulf War Related Syndromes Leading to Diagnosis and Treatment
Symptoms and General Health	Symptoms; Exposure;	DoD-057	Physiologic Effects of Stress in Gulf War Veterans
Symptoms and General Health	Symptoms; Exposure;	DoD-133	Odors, Deployment Stress, and Health: A Conditioning Analysis of Gulf War Syndrome
Symptoms and General Health	Diagnosis; Symptoms;	DoD-087	Measurement and Validation of Psychosocial Risk and Resilience Factors Accounting for Physical and Mental Health and Health-Related Quality of Life among PGWVs
Symptoms and General Health	Treatment; Symptoms;	DoD-125	A Randomized Clinical Trial of Cognitive-Behavioral Treatment for PTSD in Women (See VA-74)
Symptoms and General Health	Diagnosis; Symptoms;	DoD-131	Magnetic Resonance and Spectroscopy of the Human Brain in Gulf War Illnesses
Symptoms and General Health	Diagnosis; Symptoms;	DoD-144	Psychological Health Screening: Methods and Metrics for Deployed Forces
Symptoms and General Health	Diagnosis; Symptoms;	DoD-153	Gulf War Illness Research
Symptoms and General Health	Treatment; Symptoms;	DoD-164	Efficacy of Adjunct Sleep Interventions For PTSD (EASI- PTSD)
Symptoms and General Health	Treatment; Symptoms;	VA-060	Identification and Management of Sleep Disorders in Gulf War Veterans
Symptoms and General Health	Diagnosis; Symptoms;	VA-064 B	Quantification and Validation of Structure-Function Relationships through Visuospatial Test Performance

Brain and Nervous System Function

Clinical

Research Focus	Project Focus	Project	Project Title
Symptoms and General Health	Diagnosis; Symptoms;	VA-067	Olfactory Functioning in Gulf War Veterans
Symptoms and General Health	Treatment; Symptoms;	VA-074	A Randomized Clinical Trial for Cognitive-Behavioral Treatment for PTSD in Women (See DoD-125)
Symptoms and General Health	Treatment; Symptoms;	VA-086	A Clinical Trial of Magnetic Stimulation in Depression
Symptoms and General Health	Treatment; Symptoms;	VA-087	Improving Outcomes of Depression in Primary Care
Symptoms and General Health	Treatment; Symptoms;	VA-138	Inspiratory Flow Dynamics During Sleep in GWS and the Effect of CPAP
Symptoms and General Health;	Symptoms; Environmental Toxicology	VA-008	Psychological Test Data of Gulf War Veterans Over Time Exposure;

Brain and Nervous System Function

Development

Research Focus	Project Focus	Project	Project Title
Symptoms and General Health	Diagnosis	VA-113	Novel Cause of Motor Neuron Disease
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	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	Symptoms	DoD-082	Feasibility of Developing a Registry of PTSD Affected Veteran Sib Pairs
Symptoms and General Health	Symptoms	DoD-114	A Re-examination of Neuropsychological Functioning in Persian Gulf War Veterans

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	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	Symptoms	VA-110	Pain Among Gulf War Veterans: Secondary Analysis of CSP#458 Data
Symptoms and General Health	Symptoms; Diagnosis;	DoD-104	Clinical Evaluation of a Proposed New Gulf War Syndrome
Symptoms and General Health	Treatment; Prevention;	DoD-145	Early Intervention Research Program to Enhance Soldier Resilience
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	Diagnosis; Symptoms;	DoD-154	Prospective Assessment of Neurocognition in Future Gulf-deployed and Gulf-nondeployed Military Personnel: A Pilot Study
Symptoms and General Health	Diagnosis; Symptoms;	VA-088	Prospective Assessment of Neurocognition in Future Gulf-deployed and Gulf-nondeployed Military Personnel: A Pilot Study
Symptoms and General Health	Diagnosis; Symptoms;	HHS-002	Disease Cluster in a Pennsylvania Air National Guard Unit, EPI-AID 95-18

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

Brain and Nervous System Function

Mechanistic

Research Focus	Project Focus	Project	Project Title
	Symptoms	VA-120	Arginase NO Synthase and Cell Death in Amyotrophic Lateral Sclerosis
	Symptoms	VA-139	Sleep Neurobiology and Circuitry
	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
Environmental Toxicology	Symptoms; Exposure;	DoD-176	Studies on Axonal Transport in an Animal Model for Gulf War Syndrome
Environmental Toxicology; Symptoms and General Health	Symptoms; Exposure;	DoD-170	Structural MRI and Cognitive Correlates in Pest-Control Personnel from Gulf War I
Symptoms and General Health	Symptoms	DoD-080	Molecular Regulation of Corticosteroid Receptor Expression in Stress-Responsive Cells
Symptoms and General Health	Symptoms	DoD-091	Neurological and Circadian Substrates of PTSD-like Behaviors
Symptoms and General Health	Symptoms	DoD-092	Traumatic Experiences Persistently Enhance Cue-dependent Learning: Toward an Animal Model of Chronic Stress and Posttraumatic Stress Disorder
Symptoms and General Health	Symptoms	DoD-105	Neuroplasticity and Calcium Signaling in Stressed Rat Amygdala
Symptoms and General Health	Symptoms	VA-081	Stress, Pro-Inflammatory Cytokines and Coping Behavior
Symptoms and General Health	Symptoms	VA-090	Differential Gene Expression in Pathologies Associated with Neuronal Hyperexcitability: Links to Gulf War
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

Brain and Nervous System Function

Mechanistic

Research Focus	Project Focus	Project	Project Title
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
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
Symptoms and General Health	Treatment; Symptoms;	VA-100	Studies of the Blood-Brain Barrier and its Manipulation
Symptoms and General Health	Prevention;	VA-102	Cholinergic and Monoaminergic Influences on Sleep Symptoms

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

Environmental Toxicology

Clinical

Research Focus	Project Focus	Project	Project Title
Chemical Weapons	Exposure	DoD-146	Assessment of Toxicology Assay Methods and Chemical Exposures Among a Cohort of US Marines Deployed in the Gulf War
Pyridostigmine Bromide	Exposure; Prevention;	DoD-011	Male/Female Differential Tolerances to Pyridostigmine Bromide
Pyridostigmine Bromide; Brain and Nervous System Function	Exposure; Interactions; Symptoms	DoD-124	Randomized, Controlled Trial for Combination Treatment with Pyridostigmine, DEET, and Permethrin

Environmental Toxicology

Clinical

Research Focus	Project Focus	Project	Project Title
Pyridostigmine Bromide; Brain and Nervous System Function	Exposure; Interactions; Symptoms	DoD-155	Neuropsychological Functioning in Gulf War Veterans Exposed to Pesticides and Pyridostigmine Bromide
Pyridostigmine Bromide; Brain and Nervous System Function	Exposure; Symptoms;	DoD-064	Individual Differences in Neurobehavioral Effects of Pyridostigmine
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	Exposure; Diagnosis;	DoD-138	Improving Blood Monitoring of Enzymes as Biomarkers of Risk from Anticholinergic Pesticides and Chemical Warfare Agents
Chemical Weapons	Diagnosis; Exposure;	DoD-050	Toxicokinetics of 0-Ethyl S-(2-Diisopropylaminoethyl) Methylphosphonothioate [(+)-VX] in Rats, Hairless Guinea Pigs and Marmosets - Identification of Metabolic Pathways

Environmental Toxicology

Development

Research Focus	Project Focus	Project	Project Title
Chemical Weapons	Diagnosis; Exposure;	DoD-137	Low Level Exposure to Sulfur Mustard: Development of an SOP for Analysis of Albumin Adducts and of a System for Non-Invasive Diagnosis on Skin
Chemical Weapons	Diagnosis; Exposure;	DoD-167	Mass Spectrometry to Identify New Biomarkers of Nerve Agent Exposure
Symptoms and General Health	Diagnosis; Exposure;	DoD-018	Kuwait Oil Fires Troop Exposure Assessment Model (TEAM)
Symptoms and General Health	Diagnosis; Exposure;	DoD-019	Persian Gulf Veterans Health Tracking System
Symptoms and General Health	Diagnosis; Exposure;	DoD-100	Antibodies to Squalene
Symptoms and General Health	Diagnosis; Exposure; Symptoms	DoD-016	Kuwait Oil Fire Health Risk Assessment

Environmental Toxicology

Epidemiology

Research Focus	Project Focus	Project	Project Title
Chemical Weapons	Exposure; Symptoms;	DoD-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
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
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

Environmental Toxicology

Epidemiology

Research Focus	Project Focus	Project	Project Title
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; Interactions;	VA-145	Proteomic Analysis of Cellular Response to Biological Warfare Agents
	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
Brain and Nervous System Function	Exposure	DoD-175	Novel Pharmacological Approaches for Treatment of Neurotoxicity Induced by Chronic Exposure to Depleted Uranium
Brain and Nervous System Function	Interactions; Exposure; Symptoms	DoD-178	Analysis of Paraoxonase Status among US Navy Gulf War Veterans with Increased Postwar Symptoms, Psychological Morbidity and Medical Conditions
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	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; Symptoms;	VA-149	Behavior of Neural Stem Cells in a Rat Model of GWS
Brain and Nervous System Function; Chemical Weapons	Exposure; Symptoms;	DoD-022	Chronic Organophosphorus Exposure and Cognition
Brain and Nervous System Function; Immune Function	Exposure; Interactions; Symptoms	DoD-037	Neurobehavioral and Immunological Toxicity of Pyridostigmine, Permethrin, and DEET in Male and Female Rats
Brain and Nervous System Function;	Exposure	DoD-126	Blood-Brain Barrier Transport of Uranium
Brain and Nervous System Function;	Exposure; Symptoms	DoD-128	Multifactorial Assessment of Depleted Uranium Neurotoxicity
Brain and Nervous System Function;	Exposure; Symptoms;	DoD-129	Inhalation of Uranium Oxide Aerosol: CNS Deposition, Neurotoxicity, and Role in Gulf War Illness
Brain and Nervous System Function; 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
Chemical Weapons	Exposure; Diagnosis;	DoD-136	A Mechanism-Based, Molecular Fingerprint Strategy for Detecting Biomarkers of Organophosphate Exposure
Chemical Weapons; Brain and Nervous System Function	Exposure	VA-006 D	DNA Damage from Chemical Agents and Its Repair (Project IV)
Chemical Weapons; Brain and Nervous System Function	Exposure; Diagnosis;	DoD-135	Biochemical Markers for Exposure to Low Doses of Organophosphorous Exposure
Chemical Weapons; Brain and Nervous System Function	Prevention; Exposure;	DoD-051	Transgenic Engineering of Cholinesterases: Tools for Exploring Cholinergic Responses
Chemical Weapons; Brain and Nervous System Function	Exposure; Interactions; Symptoms	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

Environmental Toxicology

Mechanistic

Research Focus	Project Focus	Project	Project Title
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; Symptoms;	DoD-053	Long-Term Effects of Subclinical Exposures to Sarin
Chemical Weapons; Brain and Nervous System Function	Exposure; Symptoms;	DoD-152	Characterization of Intracellular Signaling Pathways Activated by Nerve Agents
Immune Function and Infectious	Exposure; Interactions;	HHS-007	Immunotoxicity of Dermal Permethrin and Cis-Urocanic Acid
Immune Function	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 Pyridostigmine Bromide	Exposure; Interactions;	DoD-077	Percutaneous Absorption of Chemical Mixtures Relevant to the Gulf War
Immune Function Symptoms and General Health	Exposure; Symptoms;	DoD-130	Carcinogenicity and Immunotoxicity of Embedded Depleted Uranium and Heavy-Metal Tungsten Alloys in Rodents
Pyridostigmine Bromide	Prevention; Exposure;	DoD-033	Effects of Pyridostigmine in Flinders Line Rats Differing in Cholinergic Sensitivity
Pyridostigmine Bromide	Exposure; Interactions;	DoD-010	Pyridostigmine Synergistic Toxicity Study
Pyridostigmine Bromide; Brain and Nervous System Function	Exposure; Interactions;	DoD-002	Physiological and Neurobehavioral Effects in Rodents from Exposure to Pyridostigmine, Fuels, and DEET
Pyridostigmine Bromide; Brain and Nervous System Function	Exposure; Interactions;	DoD-075	Toxic Interactions of Prophylactic Drugs and Pesticides
Pyridostigmine Bromide; Brain and Nervous System Function	Exposure; Interactions;	DoD-107	Stress, Organophosphates and Blood Brain Barrier Integrity
Pyridostigmine Bromide; Brain and Nervous System Function	Exposure; Interactions; Symptoms	DoD-078	Experimental Models of Gulf War Syndrome

Environmental Toxicology

Mechanistic

Research Focus	Project Focus	Project	Project Title
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; 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; Interactions; Symptoms	VA-080	Neurochemical and Neurobehavioral Impact of Pyridostigmine Bromide Treatment and Stress
Pyridostigmine Bromide; Brain and Nervous System Function	Exposure; Symptoms;	DoD-059	Pyridostigmine-induced Neurodegeneration: Role of Neuronal Apoptosis
Pyridostigmine Bromide; Brain and Nervous System Function	Exposure; Symptoms;	VA-049	Sensitivity to Pyridostigmine Bromide: Persistent Neural Dysfunction
Pyridostigmine Bromide; Brain and Nervous System Function	Exposure; Symptoms;	VA-106	Interoceptive Stressor Conditioning: A Model for Gulf War Illness
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	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

Environmental Toxicology

Mechanistic

Research Focus	Project Focus	Project	Project Title
Symptoms and General Health	Exposure	VA-065 D	Do Defective Gpx1 and ALDH2 Genes Increase Sensitivity to Environmental Hazards?

Environmental Toxicology

Mechanistic

Research Focus	Project Focus	Project	Project Title
Symptoms and General Health	Exposure	VA-065 D	Do Defective Gpx1 and ALDH2 Genes Increase Sensitivity to Environmental Hazards?
Symptoms and General Health	Exposure; Symptoms	DoD-160	Characterization of the Reproductive Toxicity of Depleted Uranium
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

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	VA-147	The Diagnosis and Pathogenesis of Occult Leishmaniasis
	Diagnosis; Treatment	VA-006 E	Clinical and Epidemiology Leishmania Research
Brain and Nervous System Function	Symptoms	DoD-088	Clinical Relevance of Novel Immunological Markers in PTSD
Brain and Nervous System Function	Symptoms	VA-017	Immunological Evaluation of Persian Gulf Veterans
Environmental Toxicology	Exposure; Interactions; Symptoms	DoD-106	The Role of Th1/Th2 cytokine balance in Gulf War- related illness
Symptoms and General Health	Treatment; Diagnosis;	DoD-067	Antibacterial Treatment Method Based Upon the Excretion of Dead and Decaying Spherical Bacteria
Symptoms and General Health	Symptoms; Exposure;	VA-006 B	Clinical and Neuroendocrine Aspects of Fibromyalgia (Project II)
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	Exposure; Symptoms;	DoD-042	The Symptomatic Persian Gulf Veterans Protocol: An Analysis of Risk Factors with an Immunologic and Neuropsychiatric Assessment
Symptoms and General Health	Treatment; Symptoms;	DoD-119	Antibiotic Treatment of Gulf War Veterans' Illnesses (ABT) (See also VA-55)
Symptoms and General Health	Treatment; Symptoms;	VA-055	Antibiotic Treatment of Gulf War Veterans' Illnesses (ABT) (See also DoD-119)

Immune Function and Infectious Diseases

Development

Research Focus	Project Focus	Project	Project Title
	Diagnosis	DoD-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
	Symptoms	VA-127	Interactions of the Leishmania sp. with Mammalian Cells
	Prevention; Treatment;	VA-094	The Immunology of Chronic Cutaneous Leishmaniasis
Environmental Toxicology	Exposure	DoD-151	Mechanisms and Consequences of Vaccine Effects on Th1/Th2 Balance in Gulf War Veterans
Environmental Toxicology	Exposure; Interactions;	DoD-112	Role of Respirable Saudi Arabian Sand and Pyridostigmine in the Gulf War Syndrome: An Autoimmune Adjuvant Disease?
Environmental Toxicology; Pyridostigmine Bromide	Exposure; Interactions;	DoD-076	Evaluations of Immunotoxicity due to Concurrent Exposure to DEET, Pyridostigmine, and JP-8 Jet Fuel
Environmental Toxicology; Pyridostigmine Bromide	Exposure; Interactions; Symptoms	DoD-081	Immunotoxicity due to Coexposure to DEET, Pyridostigmine, and Stress
Symptoms and General Health	Symptoms	VA-111	T Cell Responses to Multiple Immunizations and Stress
Symptoms and General Health	Treatment; Symptoms;	VA-105	Expression of the Major Surface Protease of Leishmania Chagasi

Reproductive Health

Clinical

Research Focus	Project Focus	Project	Project Title
	Symptoms	VA-053	Spouses and Children Program
Environmental Toxicology; Chemical Weapons	Symptoms	VA-047	Retrospective Verification of Mustard Gas Exposure
Immune Function	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-001 G	Epidemiologic Studies of Morbidity Among Gulf War Veterans: A Search for Etiologic Agents and Risk Factors; Study 7: Prevalence of Congenital Anomalies Among Children of Persian Gulf War Veterans
	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; Diagnosis; Symptoms	DoD-172	CNDP1 Polymorphisms and Carnosine Therapy in GWI
	Treatment; Symptoms;	DoD-171	Q10 for Gulf War Veterans
	Treatment; Symptoms;	VA-056	Birmingham's Gulf War Veterans' Illness Demonstration Clinic
	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	Symptoms	DoD-036	Fatigue in Persian Gulf Syndrome-Physiologic Mechanisms
Brain and Nervous System Function	Symptoms	DoD-041	Evaluation of Muscle Function in Persian Gulf Veterans
Brain and Nervous System Function	Symptoms	DoD-058	Illness Among Persian Gulf War Veterans: Case Validation Studies
Brain and Nervous System Function	Symptoms	DoD-085	CNS Cytokines and CRH in Gulf War Veterans with Multiple Unexplained Symptoms
Brain and Nervous System Function	Symptoms	DoD-101	Mechanisms in Chronic Multisymptom Illnesses
Brain and Nervous System Function	Symptoms	VA-069	Cardiovascular Hyporeactivity and Fatiguing Illness in Gulf War Veterans
Brain and Nervous System Function	Symptoms	VA-071	Central Nervous System Modulation of Visceral Pain in the Persian Gulf Syndrome
Brain and Nervous System Function	Symptoms	VA-073	Pain Sensitivity in Gulf War Veterans with Medically Unexplained Musculoskeletal Pain
Brain and Nervous System Function	Symptoms	VA-082	Pituitary Adrenal Function in People with Fatiguing Illness
Brain and Nervous System Function	Symptoms	VA-096	Functional Imaging of Pain in Veterans with Unexplained Muscle Pain
Brain and Nervous System Function	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	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
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- Modal Therapy in Veterans with Gulf War Illnesses (EBT) (See also VA-62; formerly VA/DoD 1D)
Brain and Nervous System Function	Treatment; Symptoms;	DoD-173	A Randomized, Double-Blind, Placebo-Controlled, Crossover Trial of Mifepristone in Gulf War Veterans with Chronic Multisymptom Illness
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-Modal Therapy in Veterans with Gulf War Illness (EBT) (See also DoD-115; formerly VA/DoD 1V)
Brain and Nervous System Function	Treatment; Symptoms;	VA-108	Telemedicine Treatment for Veterans with Gulf War Illness
Brain and Nervous System Function;	Diagnosis; Symptoms;	DoD-031	Dysregulation of the Stress Response in the Persian Gulf Syndrome
Environmental Toxicology	Treatment	DoD-177	Randomized Trial of an Environmental Medicine Approach to Gulf War Veterans' Illness

Symptoms and General Health

Development

Research Focus	Project Focus	Project	Project Title
	Treatment; Symptoms;	DoD-169	Development of Novel Therapy for Chronic Neuropathic Pain
Brain and Nervous System Function	Diagnosis; Symptoms;	DoD-168	Developing Biomarkers for Fibromyalgia

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	DoD-098	Investigation of a Baseline Medical Database to Evaluate the Health of Military Forces and Veterans
	Prevention	DoD-110	Predictors of Career and Family Dysfunction in Young Adults Enlisting in the United States Navy
	Symptoms	DoD-116 B	Patterns of Pre-Persian Gulf War Illness and Health Care Seeking, Pilot Study (See also VA-63B; formerly VA/DoD- 2DB)
	Symptoms	DoD-120	Assessing the Potential Health Impact of the Gulf War on Saudi Arabia National Guard Members and Their Dependents
	Diagnosis	DoD-140	US Department of Defense Surveillance for Neoplasms in Infancy
	Symptoms	DoD-148	Predicting Operational Readiness for Deployed Army National Guard and Army Reserve Soldiers and Families
	Symptoms	DoD-150	Validation Study of Gulf War Deployment Files

Symptoms and General Health

Epidemiology

Research Focus	Project Focus	Project	Project Title
	Symptoms	HHS-001	Health Assessment of Persian Gulf War Veterans from Iowa
	Prevention	HHS-009	Improving Health Risk Communications to Prevent Unexplained Illnesses Related to Military Deployments
	Symptoms	HHS-011	Deployment to the Gulf War and the Subsequent Development of Cancer
	Symptoms	VA-002	National Health Survey of Persian Gulf Veterans
	Symptoms	VA-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;	DoD-073	Post-deployment Morbid Stress, Behavior and Health:
	Exposure;		Developing a Model for Predicting Morbidity, Mortality, and Other Adverse Outcomes
	Prevention; Symptoms;	DoD-108	Health Status of Current National Guard Members
	Prevention; Symptoms;	DoD-117	Patterns of Pre-Persian Gulf War Illness and Health Care Seeking
	Prevention; Treatment;	HHS-010	Health-e Voice: Optimized Implementation of a Stepped Clinical Risk Communications Guideline
;	Symptoms	DoD-015	Comparative Mortality Among US Military Personnel Worldwide During Operations Desert Shield and Desert Storm
;	Prevention	DoD-102	Case-Control Study of Fatal Motor Vehicle Crashes Among Gulf War and Non-Deployed Veterans
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
;	Symptoms;	VA-001	Mortality Follow-up Study of Persian Gulf Veterans
Brain and Nervous System Function	Symptoms	DoD-141	Physical, Mental, Social, and Family Health Outcomes of Gulf War Veterans

Symptoms and General Health

Epidemiology

Research Focus	Project Focus	Project	Project Title
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)
Other Topics		VA-148	Profile of GW Veterans Who Applied for Undiagnosed Illness Compensation
Reproductive Health	Symptoms	DoD-030	Epidemiological Studies Persian Gulf War Illnesses, PG Women's Health Linkage Study
Reproductive Health	Symptoms; Diagnosis; Prevention	DoD-096	Deployment Health Center
Reproductive Health	Symptoms; Prevention;	DoD-001	Naval Health Study Program

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

Symptoms and General Health

Mechanistic

Research Focus	Project Focus	Project	Project Title
Environmental Toxicology	Exposure; Symptoms;	DoD-174	Autonomic Biomarkers and Treatment for Gulf War Illness
Immune Function	Symptoms	VA-132	Immunologic Mechanisms and Biomarkers in Gulf War Illness
Immune Function	Symptoms	VA-133	Longitudinal Study of Gene Expression and Gene Products in Veterans with Gulf War Illness

Appendix C
Project Funding

(As of September 30, 2007)

NOTES ON REVISED TABLE OF SPENDING FOR GULF WAR VETERANS' ILLNESSES RESEARCH FROM FY 1998-2007

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 1992-2007 are listed, only the financial data for FY 1998-2007 (a 10-year window) are shown in Appendix C; Totals for FY '98-'07 do not include funds obligated in FY 1992-1998. Projects that received all of their obligated funds prior to FY 1998 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 1998	FY 1999	FY 2000	FY 2001	FY 2002	FY2003	FY 2004	FY 2005	FY 2006	FY 2007	TOTALS FY 98-07
DoD-001	Naval Health Study Program	C	$2,654,000										$2,654,000
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	C											$0
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.	C											$0
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	C											$0
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	C											$0
DoD-001E	Epidemiologic Studies of Morbidity Among Gulf War Veterans: A Search for Etiologic Agents and Risk Factors; Study 5: Seabee Health Study	C											$0
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	C											$0
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
DoD-004	The General Well-Being of Gulf War Era Service Personnel from the States of Pennsylvania and Hawaii: A Survey	C											$0
DoD-007A	Health Risk Assessment of Embedded Depleted Uranium: Behavior, Physiology, Histology, and Biokinetic Modeling	C	$0										$0

*****Totals for FY '98 -'07 do not include funds obligated in FY 1992 -1997

Status: C=Complete; O=Ongoing

Department of Defense Gulf War Research Funding

PROJECT NO	PROJECT TITLE	STATUS	FY 1998	FY 1999	FY 2000	FY 2001	FY 2002	FY2003	FY 2004	FY 2005	FY 2006	FY 2007	TOTALS FY 98-07
DoD-007B	Carcinogenicity of Depleted Uranium Fragments	C	$0	$121,400	$0								$121,400
DoD-008	Program DoD-8.	C	$694,000	$0									$694,000
DoD-008A	Serologic Diagnosis of Viscerotropic Leishmaniasis (VTL)	C											$0
DoD-008B	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
DoD-010	Pyridostigmine Synergistic Toxicity Study	C											$0
DoD-011	Male/Female Differential Tolerances to Pyridostigmine Bromide	C	$0										$0
DoD-013	Effects of Persian Gulf War Service on Military Working Dogs	C	$120,000	$200,000	$0	$0	$0	$0					$320,000
DoD-014	Risk Factors Among US Army Soldiers for Enrolling on the Department of Veterans Affairs Gulf War Registry	C											$0
DoD-015	Comparative Mortality Among US Military Personnel Worldwide During Operations Desert Shield and Desert Storm	C											$0
DoD-016	Kuwait Oil Fire Health Risk Assessment	C											$0
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	$290,000	$295,000	$295,000	$306,000	$195,000	$225,000					$1,606,000
DoD-019	Persian Gulf Veterans Health Tracking System	C	$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
DoD-022	Chronic Organophosphorus Exposure and Cognition	C	$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											$0
DoD-030	Epidemiological Studies Persian Gulf War Illnesses, PG Women's Health Linkage Study	C	$0	$0	$0	$0							$0
DoD-031	Dysregulation of the Stress Response in the Persian Gulf Syndrome	C	$0	$0	$0								$0
DoD-032	Neuropsychological Functioning in Persian Gulf Era Veterans	C	$0	$0									$0

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Department of Defense Gulf War Research Funding

PROJECT NO	PROJECT TITLE	STATUS	FY 1998	FY 1999	FY 2000	FY 2001	FY 2002	FY2003	FY 2004	FY 2005	FY 2006	FY 2007	TOTALS FY 98-07
DoD-033	Effects of Pyridostigmine in Flinders Line Rats Differing in Cholinergic Sensitivity	C	$0	$0									$0
DoD-034	Characterization of Emissions from Heaters Burning Leaded Diesel Fuel in Unvented Tents	C	$0	$0									$0
DoD-035	Feasibility of Investigating Whether There is a Relationship Between Birth Defects and Service in the Gulf War.	C	$0	$10,500	$0	$0							$10,500
DoD-036	Fatigue in Persian Gulf Syndrome-Physiologic Mechanisms	C	$0	$0									$0
DoD-037	Neurobehavioral and Immunological Toxicity of Pyridostigmine, Permethrin, and DEET in Male and Female Rats	C	$0	$0									$0
DoD-038	Diagnostic Antigens of Leishmania tropica	C	$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	$155,000	$0	$124,868	$0							$279,868
DoD-040	Psychological and Neurobiological Consequences of the Gulf War Experience	C	$0	$0	$0	$0							$0
DoD-041	Evaluation of Muscle Function in Persian Gulf Veterans	C	$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
DoD-044	Investigation of Seminal Plasma Hypersensitivity Reactions	C	$5,000	$14,200									$19,200
DoD-045	Air Force Women's Health Surveillance Study	C	$456,732	$20,505	$0	$99,628	$0						$576,865
DoD-046	Exploratory Data Analysis with the CCEP Database	C											$0
DoD-047	Study of Mycoplasmal Infections in Gulf War Veterans	C	$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
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

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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	C	$0	$0									$0
DoD-051	Transgenic Engineering of Cholinesterases: Tools for Exploring Cholinergic Responses	C	$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	$0	$0	$217,137	$0							$217,137
DoD-054	Assessment of Subchronic Neurobehavioral and Neuropathologic Effects in Rats Following Low-Level Sarin Exposure	C	$0	$0	$0								$0
DoD-055	Low-Level Exposure to GB Vapor in Air: Diagnosis/Dosimetry, Lowest Observable Effect Levels, Performance-Incapacitation, and Possible Delayed Effects	C	$0	$0	$0	$0							$0
DoD-056	Low-Level Sarin Neurotoxicity and Its Modulation by Pyridostigmine	C	$0	$0	$0	$0							$0
DoD-057	Physiologic Effects of Stress in Gulf War Veterans	C	$0	$0	$0	$0	$0						$0
DoD-058	Illness Among Persian Gulf War Veterans: Case Validation Studies	C	$0	$0	$4,264	$267,337	$0	$0	$0				$271,601
DoD-059	Pyridostigmine-induced Neurodegeneration: Role of neuronal Apoptosis	C	$0	$0	$0	$0							$0
DoD-060	Butyrylcholinesterase Genetic Variants in Persons with Gulf War Illness	C	$0	$0									$0
DoD-061	Neurophysiologic and Neuropathologic Effects in Monkeys of Low Level Exposures to Sarin, Pyridostigmine, Pesticides, and Botulinum Toxoid	C	$0	$0	$0								$0
DoD-062	Sarin and Pyridostigmine Interaction under Physical Stress: Neurotoxic Effects in Mice	C	$0	$0									$0
DoD-063	PGW Veterans: Epidemiological and Clinical Evidence for Residual Organophosphate Neurotoxicity	C	$0	$0	$0								$0
DoD-064	Individual Differences in Neurobehavioral Effects of Pyridostigmine	C	$18,516	$0	$190,595	$0							$209,111
DoD-065	Multi-disciplinary Pathophysiologic Studies of Neurotoxic Gulf War Related Syndromes Leading to Diagnosis and Treatment	C	$0	$0	$0	$0							$0

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DoD-066	Testing for mycoplasmal infection replicability of nucleoprotein gene tracking and forensic polymerase chain reaction	C	$40,000	$403,000	$140,319	$0							$583,319
DoD-067	Antibacterial Treatment Method Based Upon the Excretion of Dead and Decaying Spherical Bacteria	C	$0	$0									$0
DoD-069	Five Year Follow-Up of Army Personnel Exposed to Chemical Warfare Agents	C	$0	$0	$110,000	$0	$245,910	$0	$0	$0	$0		$355,910
DoD-070	War Syndromes from 1900 to the Present: Symptom Patterns and Long-term Health Outcomes	C	$0	$115,000	$0	$0							$115,000
DoD-071	A Comparison of Post Deployment Hospitalization Between Vietnam and Gulf War Veterans	C	$0	$0	$0								$0
DoD-072	Long-term Effects of Subchronic Exposure to Sarin, Alone and with Stress or Other Chemicals	C	$0	$0	$0	$0	$0						$0
DoD-073	Post-deployment Morbid Stress, Behavior and Health: Developing a Model for Predicting Morbidity, Mortality, and other Adverse Outcomes	C	$0	$0	$0	$0							$0
DoD-074	Relationship of Stress Exposures to Health in Gulf War Veterans	C	$1,991,330	$0	$0	$0	$0						$1,991,330
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	$0	$0	$0								$0
DoD-080	Molecular Regulation of Corticosteroid Receptor Expression in Stress-Responsive Cells	C	$0	$0	$0	$0	$0						$0
DoD-081	Immunotoxicity due to Coexposure to DEET, Pyridostigmine, and Stress	C	$0	$0	$0	$0	$0						$0
DoD-082	Feasibility of Developing a Registry of PTSD Affected Veteran Sib Pairs	C	$0	$0	$0	$0	$0						$0
DoD-083	Risk for Stress-related Substance Abuse: the Effects of Family History of Alcoholism	C	$0	$0	$0	$0	$0						$0
DoD-084	Psychobiologic Alterations in Persian Gulf War Veterans with and without PTSD	C	$0	$0	$0	$0	$0						$0

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DoD-085	CNS Cytokines and CRH in Gulf War Veterans with Multiple Unexplained Symptoms	C	$149,200	$0	$0	$0	$0						$149,200
DoD-086	Effects of Combat Stress on Structure and Function of the Hippocampus	C	$297,800	$0	$0	$0	$0	$0					$297,800
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	$0	$0	$0	$68,044	$0	$0					$68,044
DoD-088	Clinical Relevance of Novel Immunological Markers in PTSD	C	$0	$0	$0	$0	$0						$0
DoD-089	Limbic Blood Flow and Opiate Receptor PET in Posttraumatic Stress Disorder	C	$0	$0	$0	$0	$0						$0
DoD-090	SPECT Benzodiazepine Receptor and MR Imaging in PTSD	C	$100,000	$0	$0	$0	$0						$100,000
DoD-091	Neurological and Circadian Substrates of PTSD-like Behaviors	C	$299,000	$0	$0	$0							$299,000
DoD-092	Traumatic Experiences Persistently Enhance Cue-dependent Learning: Toward an Animal Model of Chronic Stress and Posttraumatic Stress Disorder	C	$0	$0	$0	$0	$0						$0
DoD-093	Troops Exposed to Nerve Agents at Aberdeen Proving Ground: Follow-Up	C		$970,700	$0	$0							$970,700
DoD-094	Combined Analysis of the VA and DoD Gulf War Clinical Registries: A Study of Clinical Findings from Systematic Medical Examinations of 100,000 U.S. Gulf War Veterans	C		$557,173	$206,727	$0	$0						$763,900
DoD-095	Development of Diagnostic tools and alternative treatment drugs for Leishmania	C		$1,500,000	$1,500,000	$1,500,000	$1,500,000						$6,000,000
DoD-096	Deployment Health Center	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	$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

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DoD-100	Antibodies to Squalene	O		$582,756	$0	$50,000	$487,333	$0	$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	$0	$20,833,658
DoD-102	Case-Control Study of Fatal Motor Vehicle Crashes Among Gulf War and Non-Deployed Veterans	C		$249,908	$0	$253,793	$0	$281,950					$785,651
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	$166,570	$1,875,192
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
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					$1,500,000
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)	C											$0

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DoD-116B	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
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	$250,000	$25,000	$25,000	$15,000							$315,000
DoD-122	Carcinogenic Potential of Depleted Uranium and Tungsten Alloys	C	$25,000	$25,000	$30,000	$35,000							$115,000
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	$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	$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	$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	$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	$0	$5,877,526
DoD-132	Impaired Auditory Sensory Gating, Acoustic Startle Response: Effects of Long and Short Deployments on Army Combat Readiness	C				$792,198	$0	$0	$0	$0	$0		$792,198

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DoD-133	Odors, Deployment Stress, and Health: A Conditioning Analysis of Gulf War Syndrome	C				$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	$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	C				$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	$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	C				$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)	C						$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	$3,251,000	$18,224,000
DoD-144	Psychological Health Screening: Methods and Metrics for Deployed Forces	O		$109,000	$295,000	$250,000	$300,000		$0	$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	$0	$800,000
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	C	$200,000	$190,000	$260,000	$412,000	$696,111	$292,530	$0	$0	$0		$2,050,641
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	C				$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

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DoD-151	Mechanisms and Consequences of Vaccine Effects on Th1/Th2 Balance in Gulf War Veterans	C					$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	$0	$0	$0	$0	$2,019,440
DoD-153	Gulf War Illness Research	C				$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	O					$100,000	$566,542	$368,687	$604,372	$0	$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	$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	$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 Damage To Offspring	C				$382,829	$0	$0	$0	$0	$0		$382,829
DoD-159	Neurotoxicity from Chronic Exposure to Depleted Uranium	C				$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	$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	$0	$1,041,751
DoD-163	Neuroimmune Effects of Inhaling Low Dose Sarin	O						$1,828,876	$0	$0	$0	$0	$1,828,876
DoD-164	Efficacy of Adjunct Sleep Interventions For PTSD (EASI-PTSD)	O								$999,623	$0	$0	$999,623
DoD-165	Biomarkers for Amyotrophic Lateral Sclerosis in Active Duty Military - BALSAM	O								$1,000,799	$0	$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	$0	$1,000,000
DoD-167	Mass Spectrometry to Identify New Biomarkers of Nerve Agent Exposure	O									$637,848	$0	$637,848
DoD-168	Developing Biomarkers for Fibromyalgia	O									$936,067	$0	$936,067
DoD-169	Development of Novel Therapy for Chronic Neuropathic Pain	O									$840,574	$0	$840,574

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Department of Defense Gulf War Research Funding

PROJECT NO	PROJECT TITLE	STATUS	FY 1998	FY 1999	FY 2000	FY 2001	FY 2002	FY2003	FY 2004	FY 2005	FY 2006	FY 2007	TOTALS FY 98-07
DoD-170	Structural MRI and Cognitive Correlates in Pest-Control Personnel from Gulf War I	O									$208,353	$0	$208,353
DoD-171	Q10 for Gulf War Veterans	O									$718,261	$0	$718,261
DoD-172	CNDP1 Polymorphisms and Carnosine Therapy in GWI	O									$831,200	$0	$831,200
DoD-173	A Randomized, Double-Blind, Placebo-Controlled, Crossover Trial of Mifepristone in Gulf War Veterans with Chronic Multisymptom Illness	O									$650,279	$0	$650,279
DoD-174	Autonomic Biomarkers and Treatment for Gulf War Illness	O									$687,530	$0	$687,530
DoD-175	Novel Pharmacological Approaches for Treatment of Neurotoxicity Induced by Chronic Exposure to Depleted Uranium	O									$767,061	$0	$767,061
DoD-176	Studies on Axonal Transport in an Animal Model for Gulf War Syndrome	O									$112,500	$0	$112,500
DoD-177	Randomized Trial of an Environmental Medicine Approach to Gulf War Veterans' Illness	O									$445,865	$0	$445,865
DoD-178	Analysis of Paraoxonase Status among US Navy Gulf War Veterans with Increased Postwar Symptoms, Psychological Morbidity and Medical Conditions	O									$73,153	$0	$73,153
	TOTAL DOD FUNDS		$13,213,232	$22,674,338	$23,857,679	$31,587,006	$18,827,819	$16,419,497	$10,841,111	$10,091,848	$10,128,261	$3,417,570	$161,058,361

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Status: C=Complete; O=Ongoing

Department of Health and Human Services Gulf War Research Funding

PROJECT NO	PROJECT TITLE	STATUS	FY 1998	FY 1999	FY 2000	FY 2001	FY 2002	FY2003	FY 2004	FY 2005	FY 2006	FY 2007	TOTALS FY 98-07
HHS-001	Health Assessment of Persian Gulf War Veterans from Iowa	C	$0	$162,000	$0	$0							$162,000
HHS-002	Disease Cluster in a Pennsylvania Air National Guard Unit, EPI-AID 95-18	C	$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										$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						$1,818,000
HHS-006	Defining Gulf War Illness	C	$600,000	$480,000	$719,792	$200,000	$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	$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	$0	$1,381,177
HHS-011	Deployment to the Gulf War and the Subsequent Development of Cancer	O						$164,291	$0	$0	$0	$0	$164,291
HHS-012	Genetic Epidemiology of ALS in Veterans	O							$466,126	$466,481	$455,587	$441,974	$1,830,168
	TOTAL HHS FUNDS		**$1,634,347**	**$1,640,378**	**$1,567,439**	**$998,870**	**$799,814**	**$964,105**	**$466,126**	**$466,481**	**$455,587**	**$441,974**	**$9,435,121**

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PROJECT NO	PROJECT TITLE	STATUS	FY 1998	FY 1999	FY 2000	FY 2001	FY 2002	FY2003	FY 2004	FY 2005	FY 2006	FY 2007	TOTALS FY 98-07
VA-001	Mortality Follow-up Study of Persian Gulf Veterans	C	$178,197	$166,848	$176,440	$171,154	$128,496	$0					$821,135
VA-002	National Health Survey of Persian Gulf Veterans	C	$0	$0	$0	$0	$0						$0
VA-002 A	VA National Survey of Persian Gulf Veterans - Phase I	C	$18,111										$18,111
VA-002 B	VA National Survey of Persian Gulf Veterans - Phase II	C	$0	$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
VA-004	Boston Environmental Hazards Research Center Program	C	$500,000	$500,000	$229,500								$1,229,500
VA-004 A	Evaluation of Cognitive Functioning of Persian Gulf Veterans	C											$0
VA-004 B	Evaluation of Neurological Functioning in Persian Gulf Veterans	C											$0
VA-004 C	Gulf War And Vietnam Veterans Cancer Incidence Surveillance	C											$0
VA-004 D	Evaluation of Respiratory Dysfunction Among Gulf War Veterans	C											$0
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	East Orange Environmental Hazards Research Center Program	C	$500,000	$500,000	$326,900								$1,326,900
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
VA-006	Core Program: Portland Environmental Hazards Research Center: Environment, Veterans Health and the Gulf War Syndrome. Core Project for Clinical and Epidemiology Research	C	$499,926	$499,098	$233,290								$1,232,314
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

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PROJECT NO	PROJECT TITLE	STATUS	FY 1998	FY 1999	FY 2000	FY 2001	FY 2002	FY2003	FY 2004	FY 2005	FY 2006	FY 2007	TOTALS FY 98-07
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	$0	$0	$0	$0						$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	$57,600	$0									$57,600
VA-011	Neuropsychological Functioning in Veterans	C											$0
VA-012	Psychological Assessment of Operation Desert Storm Returnees	C											$0
VA-013	Neurobehavioral Aspects of Persian Gulf Experiences: A Pilot Study	C											$0
VA-015	Vaccine-Mediated Immunity Against Leishmaniasis	C	$80,000	$79,400	$41,540	$114,336	$119,600	$59,800					$494,676
VA-016	Protective Immunity in Experimental Visceral Leishmaniasis	C											$0
VA-017	Immunological Evaluation of Persian Gulf Veterans	C											$0
VA-018	Chronic Gastrointestinal Illness in Persian Gulf Veterans	C											$0
VA-020	Psychological Adjustment in Operation Desert Shield/Storm Veterans	C											$0
VA-021	A Comparison of PTSD Symptomatology among Three Army Medical Units Involved in ODS	C											$0
VA-036	Stress Symptoms and Their Causal Attribution in Desert Storm Veterans	C											$0
VA-040	Musculoskeletal Symptoms in Gulf War Syndrome	C	$0	$0									$0
VA-046	Diarrhea in Persian Gulf Veterans: An Irritable Bowel-Like Disorder	C	$0	$0	$0								$0
VA-047	Retrospective Verification of Mustard Gas Exposure	C	$299,700	$299,700	$139,960								$739,360
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

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PROJECT NO	PROJECT TITLE	STATUS	FY 1998	FY 1999	FY 2000	FY 2001	FY 2002	FY2003	FY 2004	FY 2005	FY 2006	FY 2007	TOTALS FY 98-07
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
VA-053	Spouses and Children Program	C	$98,651	$51,088	$33,655	$12,934	$25,000						$221,328
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 (13)	C	$45,750	$348,225	$259,500								$653,475
VA-060	Identification and Management of Sleep Disorders in Gulf War Veterans	C	$121,125	$328,500	$246,375								$696,000
VA-061	An Epidemiological Investigation into the Occurrence of Amyotrophic Lateral Sclerosis (ALS) Among Gulf War Veterans (See also DoD-118)	C			$0	$0	$110,600						$110,600
VA-062	A Randomized, Multi-Center, Controlled Trial of Multi-Model Therapy in Veterans with Gulf War Illness (EBT) (See also DoD-115; formerly VA/DoD 1V)	C		$788,000	$3,756,826	$1,971,233	$44,250						$6,560,309
VA-063	VA/DoD Core funding of the Medical Follow-Up Agency (See also DoD-116; formerly VA/DoD-2V/2D)	C	$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
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
VA-064	Boston Environmental Hazards Research Center	C			$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	C											$0

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VA-064 B	Quantification and Validation of Structure-Function relationships through visuospatial test performance	C											$0
VA-064 C	Development of a structured neurotoxicant assessment checklist (SNAC) for clinical use in veteran populations	C											$0
VA-065	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
VA-065 C	The importance of hydrogen peroxide detoxification in cellular protection	C											$0
VA-065 Cont'	San Antonio Environmental Hazards Research Center	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	$0	$0							$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-Behavioral 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

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PROJECT NO	PROJECT TITLE	STATUS	FY 1998	FY 1999	FY 2000	FY 2001	FY 2002	FY2003	FY 2004	FY 2005	FY 2006	FY 2007	TOTALS FY 98-07
VA-080	Neurochemical and Neurobehavioral Impact of Pyridostigmine Bromide Treatment and Stress	O						$203,400	$119,818	$248,458	$253,277	$252,602	$1,077,555
VA-081	Stress, Pro-Inflammatory Cytokines and Coping Behavior	C						$193,800	$186,035				$379,835
VA-082	Pituitary Adrenal Function in People with Fatiguing Illness	C					$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	$232,458				$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	C						$24,057	$47,011				$71,068
VA-089	National Registry of Veterans with Amyotrophic Lateral Sclerosis	C						$319,229	$625,564	$799,104	$863,951		$2,607,848
VA-090	Differential Gene Expression in Pathologies Associated with Neuronal Hyperexcitability: Links to Gulf War Illness	O						$250,000	$281,000	$281,000	$449,990	$449,990	$1,711,980
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	C						$56,750	$36,080	$163,205	$127,405		$383,440
VA-094	The Immunology of Chronic Cutaneous Leishmaniasis	C							$192,204	$157,360	$202,320		$551,884
VA-095	The Role of Signal Regulatory Proteins in Astrocytomas	C						$54,158	$231,566	$238,239	$178,679		$702,642

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PROJECT NO	PROJECT TITLE	STATUS	FY 1998	FY 1999	FY 2000	FY 2001	FY 2002	FY2003	FY 2004	FY 2005	FY 2006	FY 2007	TOTALS FY 98-07
VA-096	Functional Imaging of Pain in Veterans with Unexplained Muscle Pain	O							$49,035	$128,698	$70,302	$135,127	$383,162
VA-097	Improving a mM-CSF Tumor Vaccine for Established Intracranial Gliomas	O						$99,563	$215,093	$241,957	$246,355	$134,628	$937,596
VA-098	Post-Transcriptional Gene Regulation of VEGF in Malignant Gliomas	C							$44,420	$168,600	$168,600		$381,620
VA-099	Vaccination Against Visceral Leishmaniasis with a multi-epitope vaccine	C					$65,700	$123,413	$116,896	$118,863	$117,908		$542,780
VA-100	Studies of the Blood-Brain Barrier and its Manipulation	C					$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	$112,009	$541,212
VA-102	Cholinergic and Monoaminergic Influences on Sleep	C				$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	C						$210,600	$296,657	$307,253	$317,845		$1,132,355
VA-104	Characterization of Pain Processing Mechanisms in the Irritable Bowel Syndrome	C						$114,975	$168,600	$168,600	$84,300		$536,475
VA-105	Expression of the Major Surface Protease of Leishmania Chagasi	C					$76,613	$135,628	$298,175	$119,535	$92,817		$722,768
VA-106	Interoceptive Stressor Conditioning: A Model for Gulf War Illness	C								$193,440	$198,161		$391,601
VA-107	Evaluation of Stress Response Systems in Gulf War Veterans with CMI	O								$192,766	$117,412	$210,637	$520,815
VA-108	Telemedicine Treatment for Veterans with Gulf War Illness	O								$185,714	$238,616	$224,916	$649,246
VA-109	Effects of Stress on Memory: Brain Circuits, Mechanisms and Therapeutics	O								$158,372	$306,912	$317,503	$782,787
VA-110	Pain Among Gulf War Veterans: Secondary Analysis of CSP#458 Data	C								$96,439	$48,557		$144,996
VA-111	T Cell Responses to Multiple Immunizations and Stress	C								$112,399	$112,399		$224,798
VA-112	National VA Amyotrophic Lateral Sclerosis Research Consortium	C								$1,171,208	$734,590		$1,905,798
VA-113	Novel Cause of Motor Neuron Disease	O								$166,352	$110,152	$110,152	$386,656
VA-114	Strategies in Therapeutic Development of Neurodegenerative Diseases	C								$266,950	$370,920		$637,870
VA-115	Autonomic System Changes Cause Intestinal Symptoms in Gulf War Veterans	C								$275,623	$275,623		$551,246
VA-116	Quantitative Trait Genes Controlling Circadian and Sleep Behaviors	C								$125,888	$228,734		$354,622
VA-117	Estimates of Cancer Prevalence in Gulf Veterans Using State Registries	O								$42,206	$151,740	$115,772	$309,718

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VA-118	Post War Mortality from Neurologic Diseases in Gulf Veterans, 1991-2004	O								$42,262	$160,535	$119,453	$322,250
VA-119	Patterns of Microarray Gene Expression in Gulf War Illness	O								$192,204	$168,600	$168,600	$529,404
VA-120	Arginase NO Synthase and Cell Death in Amyotrophic Lateral Sclerosis	C								$90,988	$165,116		$256,103
VA-121	Genes, Environment, and Oxidative Stress in Neurodegenerative Disorders	C								$295,938	$441,612		$737,550
VA-122	Role of Mitochondrial Oxidative Stress in ALS	C								$55,188	$271,896		$327,084
VA-123	Interactions Between Maternal Care, Stress and Pyridostigmine Bromide	O								$60,134	$48,332	$178,447	$286,913
VA-124	Early Life Determinants of Vulnerability to Pyridostigmine Bromide	C								$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	$743,778	$1,546,202
VA-126	Structural Magnetic Resonance Imaging in Gulf War-Era Veterans	O								$159,552	$165,565	$165,565	$490,682
VA-127	Interactions of the Leishmania sp. with Mammalian Cells	C								$101,216	$166,464		$267,680
VA-128	MR Tracking of Stem Cells for Replacement Therapy in ALS	C								$236,730	$236,730		$473,460
VA-129	Glucocorticoid Responsivity in Gulf War Veterans	O								$168,600	$167,164	$168,600	$504,364
VA-130	Tissue Factor and Gulf War-Associated Chronic Coagulopathies	O									$194,826	$217,055	$411,881
VA-131	Neuroendocrine Regulators and Proteomics in GW Veterans with CMI	O									$60,767	$163,579	$224,346
VA-132	Immunologic Mechanisms and Biomarkers in Gulf War Illness	O									$64,630	$112,400	$177,030
VA-133	Longitudinal Study of Gene Expression and Gene Products in Veterans with Gulf War Illness	O									$112,400	$112,400	$224,800
VA-134	Autonomic Functions of Gulf War Veterans with Unexplained Illnesses	O									$8,880	$77,640	$86,520
VA-135	Motor Neuron Function of Gulf War Veterans with Excessive Fatigue	O									$6,744	$79,242	$85,986
VA-136	Central Mechanisms Modulating Visceral Sensitivity	C									$83,288		$83,288
VA-137	Diarrhea-Predominant Irritable Bowel Syndrome in Persian Gulf Veterans	O									$161,968	$224,294	$386,262
VA-138	Inspiratory Flow Dynamics During Sleep in GWS and the Effect of CPAP	O									$226,773	$235,240	$462,013
VA-139	Sleep Neurobiology and Circuitry	C									$33,720		$33,720

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VA-140	Integrated Neuroimaging and Neuropathological Analysis of the Effects of Physical Activity on Progression and Therapy in ALS	C									$232,553		$232,553
VA-141	Genetic Analysis of an Invertebrate Model of Amyotrophic Lateral Sclerosis	C									$243,779		$243,779
VA-142	VA Gulf War Biorepository Trust	O									$991,510	$991,510	$1,983,020
VA-143	The Role of Protein Oxidation in the Progression of ALS	O									$112,400	$112,400	$224,800
VA-144	Testing the Role of Permethrin on the Progression of ALS	O									$112,400	$112,400	$224,8000
VA-145	Proteomic Analysis of Cellular Response to Biological Warfare Agents	O									$129,260	$224,800	$354,060
VA-146	Direct Delivery of Neurotoxins to the Brain by an Intranasal Route	O									$161,687	$256,159	$417,846
VA-147	The Diagnosis and Pathogenesis of Occult Leishmaniasis	C									$98,350		$98,350
VA-148	Profile of GW Veterans Who Applied for Undiagnosed Illness Compensation	O									$24,307	$71,008	$95,315
VA-149	Behavior of Neural Stem Cells in a Rat Model of GWS	O										$129,861	$129,861
VA-150	Gulf War Veterans Illnesses' Research IDIQ Contract	O										$15,000,000	$15,000,000
	TOTAL VA FUNDS		**$4,722,820**	**$9,006,155**	**$12,020,519**	**$8,576,675**	**$4,512,676**	**$5,746,467**	**$7,644,559**	**$9,484,679**	**$12,942,066**	**$21,977,047**	**$$96,633,663**

*****Totals for FY '98 -'07 do not include funds obligated in FY 1992 -1997

Status: C=Complete; O=Ongoing