

## Version of June 21, 2011 for RACGWVI



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## 1.0 EXECUTIVE SUMMARY

The first "Working Plan" for Research on Persian Gulf War Veterans' Illnesses was published in 1995 by the Persian Gulf Veterans Coordinating Board (PGVCB), some 17 years ago, and was revised and updated in 1996. The responsibility for coordinating Gulf War research passed through a number of various federal boards, committees, and such, over the ensuing years following the PGVCB. Today's Deployment Health Working Group is the successor to the PGVCB.

Since the original "Working Plan" was published in 1995-96, a number of other commissions, advisory councils, the Institute of Medicine (IOM), the Research Advisory Committee for Gulf War Veterans' Illnesses (RACGWVI), and others, have made significant contributions both monitoring, assessing, and making recommendations helpful to the ongoing work of planning and coordinating Gulf War Research across the federal government. The IOM has produced an extensive series of independent reports which chronicle and assess the results of Gulf War Research. The Research Advisory Committee for Gulf War Veterans' Illnesses (RACGWVI) has also prepared extensive reports giving its independent assessment of the results of Gulf War Research.

In 2011, the VA Office of Research and Development undertook the task of preparing the first Strategic Plan for Gulf War Research. This was because substantial advances have been made across the board in medical and scientific research since the first Gulf War "Working Plan" was put forward in 1995-96. These include mapping the human genome, advances in medical imaging, and advances in medical informatics and electronic health information, to name but three technologies that were not available in 1995-96. In addition, the results from the ongoing Gulf War research programs that were initiated after the Gulf War in VA, DoD, HHS, and elsewhere now allow us to take advantage of this specific progress in Gulf War research. This progress helps to suggest new and innovative approaches to future Gulf War research that may be most likely to bear fruit. In addition, the ensuing years have seen an increasing appreciation among federal agencies of the need for thoughtful and careful coordination of interagency research efforts. At the April 2011 meeting of the Gulf War Steering Committee, a draft outline of the proposed strategic plan was presented and discussed.

The overall goal of the *Gulf War Research Strategic Plan 2011-2015* is to improve the health and well-being of Gulf War Veterans, and to utilize emerging knowledge to prevent similar war-related illnesses in the future. In developing the *Gulf War Research Strategic Plan 2011-2015*, the most recent reports from the IOM and RACGWVI, as well as other reports and publications, were reviewed to prepare a harmonized summary of what has been accomplished to date in Gulf War research and what research remains to be done that will benefit Gulf War Veterans.

The *Gulf War Research Strategic Plan 2011-2015* thus represents a significant major revision and update of the first "Working Plan" that was put forth in 1995-96. The Plan has five major sections:

1. Executive Summary
2. Introduction and Background
3. Evolution of the Gulf War Strategic Plan 1995-2011

4. Summary of Gulf War Research Results and Federal Funding 1993-2010
5. Gulf War Strategic Research Objectives 2011-2015

The seven strategic objectives that the *Gulf War Research Strategic Plan 2011-2015* advances are presented in detail in section 5 of the Plan:

1. Research to enable development of new Gulf War Case Definitions
2. Genetics/Genomics
3. Biomarkers
4. Symptomatic and Specific Treatments
5. Coordination/Communication between Partners and Researchers
6. Translation of Research into Practice
7. Animal Models

Progress has been made in Gulf War Research, yet much work remains to be done. This *Gulf War Research Strategic Plan 2011-2015* has been formulated to make clearer the way forward in research. The *Gulf War Research Strategic Plan 2011-2015* will be reviewed annually by the Gulf War Steering Committee, and updated as needed.

## 2.0 INTRODUCTION AND BACKGROUND

### 2.1 The 1990-1991 Gulf War and the Nation's Response to the Need for Research

After Iraq's occupation of Kuwait in August 1990, the United States deployed military personnel to Southwest Asian support of Operations Desert Shield and Desert Storm. At the conclusion of the first year of operations on July 31, 1991, the United States had deployed 696,841 military personnel from all five services and National Guard to the Kuwaiti Theater of Operations (KTO).

During and after their return from the KTO, a significant proportion of Gulf War Veterans reported a range of chronic symptoms and health problems at rates that exceeded the rates for non-deployed era Veterans. These symptoms included: persistent headaches, joint pain, fatigue, muscle pain, attention and memory (cognitive) problems, gastrointestinal difficulties, sleep disturbances, and skin abnormalities. While some of these ill Veterans meet case definition(s) for other chronic multisymptom illnesses such as chronic fatigue syndrome or fibromyalgia, the majority have defied exact diagnosis.

On August 31, 1993, pursuant to Public Law 102-585, President Clinton named the Secretary of Veterans Affairs to coordinate research on the health consequences of service in the Gulf War. VA initially carried out its coordinating role through the auspices of the Persian Gulf Interagency Research Coordinating Council (PGIRCC). On January 21, 1994, the Secretaries of DOD, HHS, and VA announced the establishment of the Persian Gulf Veterans Coordinating Board (PGVCB) to coordinate efforts to resolve the health concerns of Gulf War Veterans. PGVCB developed three mission objectives, and assigned each to a separate working group: the Clinical Working Group, the Research Working Group, and the Disability and Benefits Working Group. The Research Working Group (RWG) subsumed PGIRCC responsibilities.

In 1995, the PGVCB developed a contextual framework for evaluating research related to military service in the 1990-1991 Gulf War. To that end, the PGVCB identified 19 major epidemiological research questions and subsequently added two additional questions in 1996. This framework was published as the "Working Plan for Research on Persian Gulf War Veterans' Illnesses" and has served as the guiding principles for Gulf War Research up to the present day. The comprehensive Federal Gulf War research portfolio has addressed each of these 21 questions, and relevant results have been published on each one; the status of the 21 questions is listed in section 4 of this report. The Medical and Veterans Health Coordinating Board (MVHCB), the successor organization to the PGVCB, conducted a comprehensive assessment of the progress made on each of these 21 questions in the Annual Report to Congress for 2000. 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. Based on the 2006 Institute of Medicine (IOM) review of the scientific literature on infectious diseases, the DHWG removed 2 of the 21 questions (numbers 2 and 19) from the Working Plan in 2006 as being "answered" and no longer in need of further research (see the Annual Report to Congress for 2006). The Research Topics were then organized into five major categories is presented below:

- (1) Brain & Nervous System Function
- (2) Environmental Toxicology
- (3) Immune Function
- (4) Reproductive Health
- (5) Symptoms and General Health Status

To date, VA, the Department of Defense, and the Department of Health and Human Services have funded 370 research projects pertaining to the health consequences of military service in the 1990-1991 Gulf War, as reported annually to Congress.

## 2.2 Gulf War Research Strategic Plan 2011-2015

The *Gulf War Research Strategic Plan 2011-2015* is the most recent and substantial revision of the original "Working Plan" put forth in 1995-96. Those who formulated this original "Working Plan" envisioned that it would be a "living document" needing revision over time as new results and findings were discovered by both Gulf War researchers and researchers in other fields.

The *Gulf War Research Strategic Plan 2011-2015* will be reviewed annually by the Gulf War Steering Committee to determine if modifications are needed.

## 2.3 VA Research and Development Strategic Plan: 2009-2014

The *Gulf War Research Strategic Plan 2011-2015* compliments the existing *VA Research and Development Strategic Plan: 2009-2014*, which is the strategic plan for all research in ORD. This larger strategic plan also articulates the need for more Gulf War Research. For example, "Deployment-related exposure to hazardous environmental agents" is listed as one of 10 of the priority areas for VA's Office of Research and Development. In addition, the Plan notes and cites several examples of the need for Gulf War related research, such as:

- Research in ALS related to environmental exposure,<sup>1,3</sup>
- Identification of biomarkers for different stages of illness and recovery,<sup>1,9</sup>
- Illnesses related to service in the 1990-1991 Gulf War<sup>2,2</sup>, and
- A communication portal to improve communication among VA researchers.<sup>4,8</sup>

The *VA Research and Development Strategic Plan: 2009-2014* sets four over-arching goals that apply to all VA Research, including Gulf War Research. These are:

- Advance knowledge toward improving each Veteran's health and well-being, relying on a spectrum of research including basic, translational, clinical, health services, and rehabilitative science.
- Apply advances in scientific knowledge to create, test, compare, and implement new treatments, technologies, education modules, and models of care so that Veterans receive the most effective individualized care solutions.
- Attract, train, and retain the highest-caliber investigators and staff, and nurture their continuous development as leaders in their fields.

- Assure a state-of-the-art research enterprise with a culture of professionalism, collaboration, accountability and the highest regard for research volunteers' safety and privacy.

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### 3.0 EVOLUTION OF THE GULF WAR RESEARCH STRATEGIC PLAN

Many Federal Research Agencies have policy and planning processes in place that develop documents to guide both the agency and researchers who apply to the agency for research funding. These documents are referred to by different names across agencies: "long-range plans," strategic plans, "five year plans," and the like. Whatever they are called, these plans attempt to set out guidelines or a framework for the directions of future research the agency views as its mission to pursue.

During deployment to the Gulf, and as Service members began returning from the Gulf, it became apparent that some Service members and Veterans were showing symptoms that were difficult to explain using current diagnostic criteria for illnesses. In January 1994, the Secretaries of DoD, HHS and VA announced the establishment of the Persian Gulf Veterans Coordinating Board (PGVCB) to coordinate efforts to resolve the health concerns of Gulf War Veterans.

A critical unresolved issue was whether deployed Service members were experiencing these symptoms at a higher rate than comparable non-Gulf War Service members and Veterans. In addition, many Service members and Veterans were questioning whether the illnesses that are common and diagnosable were etiologically linked to their service in the Gulf War. It became apparent to both DoD and VA that scientific and medical research would be required to address this complex issue. The question then had to be answered: "What research needs to be undertaken?" (1995-6). The PGVCB established three primary mission objectives to achieve through interagency coordination:

- Ensure all Veterans receive the complete range of health care services necessary to evaluate and treat Gulf War-related health problems;
- Develop a research program that produces a complete and accurate understanding of Gulf War-related health problems; and
- Develop clear, consistent guidelines for evaluating disabilities related to Persian Gulf service.

The PGVCB assigned these objectives to three working groups — the second of being the Research Working Group, which is the focus of this strategic plan. The Research Working Group developed a plan to ensure that all important areas of research relating to Gulf War Veterans' health issues were addressed, successfully coordinating research activities among DoD, VA, and HHS. Independent scientific panels helped evaluate research proposals. The Research Working Group analyzed the suggestions of several external oversight committees and made recommendations to the Secretaries concerning appropriate research goals. The PGVCB Research Working Group provided detailed annual research progress reports to Congress beginning in 1995-96.

The Persian Gulf Veterans Coordinating Board (PGVCB) was formed in 1993, and originally was composed of VA, DoD, HHS, and EPA. Its charge was to lead the way in the conduct of research on Persian Gulf Veterans' illnesses. In 1995 it was apparent that the scope of the research issues necessitated the development of a working plan to help the Persian Gulf Veterans Coordinating Board to coordinate federally-sponsored research in a way that all the relevant research issues would be targeted but unnecessary duplication would be avoided.

The original plan attempted to balance the need for specific, targeted research directions, with the awareness that successful research, fostered by sound research questions, arises from the minds of independent scientists in research laboratories. Therefore, the Plan set the broad research areas in which it is believed investment would most likely result in new and useful knowledge.

Although the Plan was primarily intended to guide federal decision makers in establishing research priorities, it was also meant to provide information to members of Congress, the scientific community, the public and, importantly, the Veterans of the Persian Gulf conflict, about the manner in which the federal government was carrying out this important research.

Three broad research goals were presented in the original 1995-6 Working Plan:

- Establish the nature and prevalence of symptoms, diagnosable illnesses, and unexplained conditions among Persian Gulf Veterans in comparison to appropriate control groups;
- Identify the possible risk factors for any illnesses, beyond those expected to occur, among Persian Gulf Veterans;
- Identify appropriate diagnostic tools, treatment methods, and prevention strategies for any excess illness conditions found among Persian Gulf Veterans.

The plan also identified the following areas for which significant gaps in knowledge existed at that time:

- Information on the prevalence of symptoms, illnesses, and/or diseases within other coalition forces;
- Information on the prevalence of symptoms, illnesses, and/or diseases within indigenous populations within the Persian Gulf area including Saudi Arabia and Kuwait;
- Information on the prevalence of adverse reproductive outcomes among Persian Gulf Veterans and their spouses;
- Simple and sensitive tests for *Leishmania tropica* infection that could lead to quantification of the prevalence of *L. tropica* infection among Persian Gulf Veterans; and
- Information on the long-term, cause-specific mortality among Persian Gulf Veterans.

In the revised 1996 Working Plan, twenty-one epidemiological research questions were formulated. These research questions have served as the guiding principles for federally-funded Gulf War Research up to the present day. Some of these questions have been answered. Many of the rest are likely to be answered in the coming years.

The Medical and Veterans Health Coordinating Board (MVHCB), the successor organization to the PGVCB, conducted a comprehensive assessment of the progress made on each of these 21 questions in the Annual Report to Congress for 2000. 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. The 21 Research Topics were then organized into 5 major categories as described below. Based on the 2006 Institute of Medicine (IOM) review of the scientific literature on infectious diseases, the DHWG removed 2 of the 21 questions (numbers 2 and 19)

from the Working Plan in 2006 as being “answered” and no longer in need of further research (see the Annual Report to Congress for 2006).

The 2006 Working Plan was organized into five major categories (shown in bold) with related research topics as shown below, with further detail regarding the research questions presented in section 4.1.1.

**(1) Brain & Nervous System Function**

Organic neuropsychological and neurological deficits (Question 16)

Psychological symptoms and/or diagnoses (Question 18)

**(2) Environmental Toxicology**

Petroleum products and combustion products (Question 3)

Occupational/environmental hazards (Question 4)

Organophosphorus nerve agent and/or sulfur mustard from bombing at Muhammadiyat or weapons bunker at Khamisiyah (Question 5)

Chemical agents, other than at Khamisiyah (Question 6)

Pyridostigmine bromide and other medical prophylaxes (e.g. vaccines and anti-malarials) (Question 7)

Psychophysiological stressors (Question 8)

Short term, low level exposures to pyridostigmine bromide, DEET, or permethrin, alone or in combination as a cause of short-term and/or long-term neurological effects (Question 17)

**(3) Immune Function and Infectious Diseases**

~~Leishmania tropica (Question 2) (removed)~~

Altered immune function or host defense (Question 10)

~~Other infectious diseases (Question 19) (removed)~~

**(4) Reproductive Health**

Birth defects in offspring (Question 11)

Lower reproductive success (Question 12)

Sexual dysfunction (Question 13)

**(5) Symptoms and General Health Status**

Increased prevalence or severity of symptoms and/or illnesses (Question 1)

Nonspecific symptoms and symptom complexes (e.g., chronic multisymptom illnesses) (Question 9)

Changes in lung function or airway reactivity (Question 14)

Smaller baseline lung function or greater degree of nonspecific airway reactivity (Question 15)

Development of cancers of any type (Question 20)

## Mortality rates (Question 21)

These research questions are presented in detail in Section 4.0, with brief descriptions about the current status of each research question.

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## 4.0 SUMMARY OF GULF WAR RESEARCH RESULTS AND PAST FEDERAL RESEARCH SUPPORT

### 4.1 Summary of Gulf War Research Results 1993-2011

The most recent evaluation of the results of Gulf War Research was by the IOM (vol 8). The IOM is generally regarded as the "Gold Standard" with respect to evaluating the results of research programs that are published in the peer reviewed literature, including publications resulting from federally-funded research programs across agencies. VA first contracted with the IOM in 2000. Since then, IOM has prepared many Gulf War-related reports, up to the most recent report in 2010 entitled *Gulf War and Health: Volume 8: Update of Health Effects of Serving in the Gulf War*. This series of reports from the IOM remain the most consistent and independent assessments available for the actual results of all Gulf War research programs from 1995 to the present.

These IOM assessments are used by the VA and other federal agencies to help determine and reassess the extent to which the collective findings of completed Gulf War Illnesses research projects have in fact addressed key Gulf War Research questions, and whether research questions being investigated remain relevant. The IOM report of 2010 is an independent, thorough and comprehensive analysis of past Gulf War Research results across the VA and all federal agencies.

In addition, the most recent report of the Research Advisory Committee for Gulf War Veterans' Illnesses (RACGWVI) represents a second independent opinion on the results of Gulf War Research. In 2008, the RACGWVI issued its most current report *Gulf War Illness and the Health of Gulf War Veterans*. This report was also very comprehensive and provided additional specific research recommendations.

By carefully comparing the RACGWVI and IOM reports, as well as other information, the present *Gulf War Research Strategic Plan 2011-2015* identifies the areas of research that appear most likely to succeed in providing new information that will help Gulf War Veterans. Such a careful prioritization, based on the best knowledge available at this time, is essential when research funding has finite limits.

Examples of findings that have emerged from past research include:

- VA and DoD researchers have played a critical role in identifying the broad spectrum of symptoms affecting Gulf War Veterans and that these symptoms have persisted, even 20 years after the war. The existence and/or persistence of these chronic symptoms have been clearly documented and recognized by VA and DoD.
- To date, no general increase in cancer risk in Gulf War Veterans has been identified. One published report indicated that there may be an increased risk of brain cancer mortality in Gulf War Veterans potentially exposed to nerve agents.
- Higher mortality rates have not been identified, with the possible exception of ALS. VA continues to monitor causes of mortality in Gulf War Veterans as part of an ongoing surveillance program.
- Concerns over possible exposure to Leishmaniasis lead both VA and DoD to fund a number of projects designed to develop new diagnostic tests, and identify disease mechanisms that would lead to new treatments. Clinicians at Walter Reed Army medical Center have identified only 20 cases of cutaneous

leishmaniasis and 12 cases of visceral leishmaniasis. Following the publication of Gulf War and Health Volume 5 Infectious Diseases by the Institute of Medicine in 2006, the research portfolio on Gulf War Illnesses was re-evaluated and all projects related to leishmaniasis were “closed” in the 2006 Annual Report to Congress.

- The DU Surveillance program is operated at the Baltimore VA Medical Center to monitor Gulf War Veterans with embedded DU shrapnel. To date, no ill health effects have been reported in these Veterans.
- Results have varied, but do not suggest that major immune dysfunction is a causative factor in ill Gulf War Veterans. Although these results do not necessarily elucidate the cause of GWI, they do reveal a role for immune cell dysfunction in sustaining illness.
- Adverse reproductive outcomes are similar among GW-exposed and non-exposed pregnancies. Overall rates are still within the normal range found in the general population.
- While some studies have indicated that Gulf War Veterans are more likely to self-report pulmonary problems or to have more hospitalizations for diseases of the respiratory system (including asthma), other reports have found no increased prevalence of pulmonary symptoms or link between exposure to oil well fires and development of asthma.

#### 4.1.1 “A Working Plan for Research on Persian Gulf Veterans’ Illnesses” 1995-96: The Twenty-One Research Questions

In 1995 and 1996 the Persian Gulf Veterans Coordinating Board (now known as the Deployment Health Working Group; DHWG) published “A Working Plan for Research on Persian Gulf Veterans’ Illnesses.” As with today’s DHWG, the PGVC was the joint effort of VA, DoD and HHS. This working plan was framed as a series of 21 questions directed at the issue of whether Gulf War Veterans experience a greater prevalence of symptoms and illnesses in comparison to a control population. The questions have been re-grouped below (but with their original numbering), and comments about research results to date follow the questions. Note: Questions 2 and 19, concerning infectious diseases, were removed from the Working Plan in 2006, based on an IOM review of the scientific literature on infectious diseases.

**1. What is the prevalence of symptoms/illnesses in the Persian Gulf Veteran population? How does this prevalence compare to that in an appropriate control group?**

**9. Are Persian Gulf Veterans more likely than an appropriate comparison group to experience non-specific symptoms and symptom complexes?**

VA and DoD researchers have played a critical role in identifying the broad spectrum of symptoms affecting Gulf War Veterans and that these symptoms have persisted, even 20 years after the war. While some of these ill Gulf War Veterans have been diagnosed as having chronic fatigue syndrome or fibromyalgia, two chronic multisymptom illnesses that exist in the general population, others with chronic multiple symptoms have not met the diagnostic criteria for CFS or FM and remain in the “medically undiagnosed” category. The existence and/or persistence of these chronic symptoms have been clearly documented and recognized by VA and DoD.

**20. Do Gulf War Veterans have a greater risk of developing cancers of any type when compared with an appropriate control population? –**

To date, no general increase in cancer risk has been identified. One published report indicated that there may be an increased risk of brain cancer mortality in Gulf War Veterans potentially exposed to nerve agents.

*Neurological mortality among U.S. Veterans of the Persian Gulf War: 13-year follow-up.* Barth SK, Kang HK, Bullman TA, Wallin MT. Am J Ind Med. 2009 Jul 7. [Epub ahead of print]

*Mortality in US Army Gulf War Veterans exposed to 1991 Khamisiyah chemical munitions destruction.* Bullman TA, Mahan CM, Kang HK, Page WF. Am J Public Health. 2005 Aug;95(8):1382-8.

*Illness experience of Gulf War Veterans possibly exposed to chemical warfare agents.* McCauley LA, Lasarev M, Sticker D, Rischitelli DG, Spencer PS. Am J Prev Med. 2002 Oct;23(3):200-6.

**21. Are Gulf War Veterans experiencing a higher mortality rate than that of an appropriate control population? Are specific causes of death related to service in the Persian Gulf region?**

Higher mortality rates have not been identified, with the possible exception of ALS. VA continues to monitor causes of mortality in Gulf War Veterans as part of an ongoing surveillance program.

*Neurological mortality among U.S. Veterans of the Persian Gulf War: 13-year follow-up.* Barth SK, Kang HK, Bullman TA, Wallin MT. Am J Ind Med. 2009 Jul 7. [Epub ahead of print]

*Healthcare utilization and mortality among Veterans of the Gulf War.* Gray GC, Kang HK. Philos Trans R Soc Lond B Biol Sci. 2006 Apr 29;361(1468):553-69.

*Prospective study of military service and mortality from ALS.* Weisskopf MG, O'Reilly EJ, McCullough ML, Calle EE, Thun MJ, Cudkovic M, Ascherio A. Neurology. 2005 Jan 11;64(1):32-7.

*Mortality in US Army Gulf War Veterans exposed to 1991 Khamisiyah chemical munitions destruction.* Bullman TA, Mahan CM, Kang HK, Page WF. Am J Public Health. 2005 Aug;95(8):1382-8.

*Mortality among US and UK Veterans of the Persian Gulf War: a review.* Kang HK, Bullman TA, Macfarlane GJ, Gray GC. Occup Environ Med. 2002 Dec;59(12):794-9. Review.

*Mortality among US Veterans of the Persian Gulf War: 7-year follow-up.* Kang HK, Bullman TA. Am J Epidemiol. 2001 Sep 1;154(5):399-405.

**2. What was the overall exposure of troops to Leishmania tropica?**

**19. What is the prevalence of Leishmaniasis and other infectious diseases in the Gulf War Veteran population?**

Concerns over possible exposure to Leishmaniasis lead both VA and DoD to fund a number of projects designed to develop new diagnostic tests, and identify disease mechanisms that would lead to new treatments. Clinicians at Walter Reed Army medical Center have identified only 20 cases of cutaneous leishmaniasis and 12 cases of visceral leishmaniasis. Following the publication of Gulf War and Health Volume 5 Infectious Diseases by the Institute of Medicine in 2006, the research portfolio on Gulf War Illnesses was re-evaluated and all projects related to leishmaniasis were "closed" in the 2006 Annual Report to Congress. Although many of these projects remained ongoing, the closed status allowed the funding for these projects to no longer be counted as part of the Gulf War research effort; these projects remained as part of the Federal research portfolio on health issues related to the current conflicts in Iraq and Afghanistan.

**3. What were the exposure concentrations to various petroleum products, and their combustion products, in typical usage during the Persian Gulf conflict?**



- 4. What was the extent of exposure to specific occupational/environmental hazards known to be common in the Persian Gulf Veterans' experience? Was this exposure different from that of an appropriate control group?**
- 5. What were the potential exposures of troops to organophosphorus nerve agent and/or sulfur mustard as a result of allied bombing at Muhammadiyat and Al Muthanna, or the demolition of a weapons bunker at Khamisiyah?**
- 6. What was the extent of exposure to chemical agent, other than at Khamisiyah, in the Persian Gulf as a function of space and time?**
- 7. What was the prevalence of pyridostigmine (PB) use among Persian Gulf troops?**
- 17. Can short-term, low-level exposures to pyridostigmine bromide, the insect repellent DEET, and the insecticide permethrin, alone or in combination, cause short-term and/or long-term neurological deficits?**

A number of VA and DoD projects were funded to model exposures to petroleum and petroleum combustion products in enclosed spaces and to collect self-reported exposure data (epidemiological studies) to help estimate exposure levels. The literature on such exposures was reviewed in 1995 by the Institute of Medicine in Gulf War and Health Volume 3 Fuels, Combustion Products, and Propellants.

VA and DoD have funded numerous research projects to examine the effects of exposure to environmental hazards known to be common in the Gulf War Theater of Operations. These include exposure to depleted uranium (DU), use of insecticides and pesticides, use of pyridostigmine bromide and multiple vaccines that were used to protect deployed troops. The DU Surveillance program is operated at the Baltimore VA Medical Center to monitor Gulf War Veterans with embedded DU shrapnel. To date, no ill health effects have been reported in these Veterans.

Several plume models were developed to estimate ground-level concentrations (exposures) of sarin and cyclosarin following the demolition of munitions at Khamisiyah. In its 2004 testimony (GAO-04-281T) before the Subcommittee on National Security, Emerging Threats, and International Relations, Committee on Government Reform, House of Representatives GAO recommended that the Secretary of Defense and the Secretary of Veterans Affairs not use the plume-modeling data for any other epidemiological studies of the 1991 Gulf War. The GAO concluded that the models were not fully developed for analyzing long-range dispersion of chemical warfare agents as an environmental hazard. The modeling assumptions as to source term data—quantity and purity of the agent—were inaccurate because they were uncertain, incomplete, and nonvalidated. The plume heights used in the modeling were underestimated and so were the hazard area. Postwar field testing used to estimate the source term did not realistically simulate the actual conditions of bombings or demolitions. Finally, the results of all models—DOD and non-DOD models—showed wide divergences as to the plume size and path.

- 8. What was the prevalence of various psychophysiological stressors among Gulf War Veterans? Is the prevalence different from that of an appropriate control group?**

**18. Do Persian Gulf Veterans have a significantly higher prevalence of psychological symptoms and/or diagnoses than do members of an appropriate control group?**

Early concerns after the 1990-1991 Gulf War prompted VA, DoD and HHS to examine psychological stressors as contributing factors in the development of symptoms in ill Gulf War Veterans. Although psychological stressors have not been shown to be correlated with development of chronic multisymptom illness in Gulf War Veterans, a number of these studies have identified PTSD and other stress-related mental illnesses in Gulf War Veterans.

**16. Is there a greater prevalence of organic neuropsychological and neurological deficits in Persian Gulf Veterans compared to appropriate comparison populations?**

Research funding to address this question focused in 2 primary areas. The first was whether there were measurable alterations in brain structure and/or nervous system function that could be correlated with the symptoms reported by ill Gulf War Veterans. Several studies recently reported finding such measurable changes in various types of brain imaging. A major focus of the UTSW Gulf War Research program was to correlate changes detected in a variety of brain imaging modalities with specific changes in neurocognitive function (i.e., memory, attention, etc.). The second was concern that deployment during the 1990-1991 Gulf War led to or contributed to an increase in the prevalence of neurological diseases such as amyotrophic lateral sclerosis (ALS) and multiple sclerosis (MS).

*Abnormal brain response to cholinergic challenge in chronic encephalopathy from the 1991 Gulf War.* Haley RW, Spence JS, Carmack PS, Gunst RF, Schucany WR, Petty F, Devous MD Sr, Bonte FJ, Trivedi MH. *Psychiatry Res.* 2009 Mar 31;171(3):207-20

*Clinical aspects of ALS in Gulf War Veterans.* Kasarskis EJ, Lindquist JH, Coffman CJ, Grambow SC, Feussner JR, Allen KD, Oddone EZ, Kamins KA, Horner RD; Als Gulf War Clinical Review Team. *Amyotroph Lateral Scler.* 2009 Feb;10(1):35-41.

*Spatial analysis of the etiology of amyotrophic lateral sclerosis among 1991 Gulf War Veterans.* Miranda ML, Alicia Overstreet Galeano M, Tassone E, Allen KD, Horner RD. *Neurotoxicology.* 2008 Nov;29(6):964-70.

*Amyotrophic lateral sclerosis among 1991 Gulf War Veterans: evidence for a time-limited outbreak.* Horner RD, Grambow SC, Coffman CJ, Lindquist JH, Oddone EZ, Allen KD, Kasarskis EJ. *Neuroepidemiology.* 2008;31(1):28-32.

*Genes and Environmental Exposures in Veterans with Amyotrophic Lateral Sclerosis: the GENEVA study. Rationale, study design and demographic characteristics.* Schmidt S, Allen KD, Loiacono VT, Norman B, Stanwyck CL, Nord KM, Williams CD, Kasarskis EJ, Kamel F, McGuire V, Nelson LM, Oddone EZ. *Neuroepidemiology.* 2008;30(3):191-204.

*Quantitative magnetic resonance brain imaging in US army Veterans of the 1991 Gulf War potentially exposed to sarin and cyclosarin.* Heaton KJ, Palumbo CL, Proctor SP, Killiany RJ, Yurgelun-Todd DA, White RF.

Neurotoxicology. 2007 Jul;28(4):761-9

*Estimating the occurrence of amyotrophic lateral sclerosis among Gulf War (1990-1991) Veterans using capture-recapture methods.* Coffman CJ, Horner RD, Grambow SC, Lindquist J; VA Cooperative Studies Program Project #500.

Neuroepidemiology. 2005;24(3):141-50.

*Prospective study of military service and mortality from ALS.* Weisskopf MG, O'Reilly EJ, McCullough ML, Calle EE, Thun MJ, Cudkowicz M, Ascherio A. Neurology. 2005 Jan 11;64(1):32-7.

*Excess incidence of ALS in young Gulf War Veterans.* Haley RW. Neurology. 2003 Sep 23;61(6):750-6.

*Occurrence of amyotrophic lateral sclerosis among Gulf War Veterans.* Horner RD, Kamins KG, Feussner JR, Grambow SC, Hoff-Lindquist J, Harati Y, Mitsumoto H, Pascuzzi R, Spencer PS, Tim R, Howard D, Smith TC, Ryan MA, Coffman CJ, Kasarskis EJ. Neurology. 2003 Sep 23;61(6):742-9.

**10. Do Persian Gulf Veterans have a greater prevalence of altered immune function or host defense when compared with an appropriate control group?**

Results have varied, but do not suggest that major immune dysfunction is a causative factor in ill Gulf War Veterans. Results from VA-131 and VA-132 indicate that GWI patients have impaired immune function, as demonstrated by decreased NK cytotoxicity and altered gene expression associated with NK cell function, pro-inflammatory cytokines, T-cell ratios, and dysregulated mediators of the stress response (including salivary cortisol) were also altered in GWI cases compared to control subjects. Although these results do not necessarily elucidate the cause of GWI, they do reveal a role for immune cell dysfunction in sustaining illness.

*Impaired immune function in Gulf War Illness.* Whistler T, Fletcher MA, Lonergan W, Zeng XR, Lin JM, Laperriere A, Vernon SD, Klimas NG. BMC Med Genomics. 2009, 2:12.

*Twenty-four hour plasma cortisol and adrenocorticotrophic hormone in Gulf War Veterans: relationships to posttraumatic stress disorder and health symptoms.* Golier JA, Schmeidler J, Legge J, Yehuda R. Biol Psychiatry. 2007 Nov 15;62(10):1175-8.

*Enhanced cortisol suppression to dexamethasone associated with Gulf War deployment.* Golier JA, Schmeidler J, Legge J, Yehuda R. Psychoneuroendocrinology. 2006 Nov;31(10):1181-9.

*Cellular and humoral immune abnormalities in Gulf War Veterans.* Vojdani A, Thrasher JD. Environ Health Perspect. 2004 Jun;112(8):840-6.

*Pyridostigmine bromide (PYR) alters immune function in B6C3F1 mice.* Peden-Adams MM, Dudley AC, EuDaly JG, Allen CT, Gilkeson GS, Keil DE. Immunopharmacol Immunotoxicol. 2004 Feb;26(1):1-15.

- 11. Is there a greater prevalence of birth defects in the offspring of Persian Gulf Veterans than in an appropriate control population?**
- 12. Have Persian Gulf Veterans experienced lower reproductive success than an appropriate control population?**
- 13. Is the prevalence of sexual dysfunction greater among Persian Gulf Veterans than among an appropriate comparison population?**

Adverse reproductive outcomes are similar among GW-exposed and non-exposed pregnancies. As noted in the 2008 report from the Research Advisory Committee for Gulf War Veterans' Illnesses (RACGWVI) there are "significant, but modest, excess rates of birth defects in children of Gulf War Veterans. Information on specific types of birth defects has been inconsistent, however, and overall rates are still within the normal range found in the general population."

*Gulf war depleted uranium risks.* Marshall AC. J Expo Sci Environ Epidemiol. 2008 Jan;18(1):95-108. Epub 2007 Feb 14.

*Depleted uranium exposure and health effects in Gulf War Veterans.* Squibb KS, McDiarmid MA. Philos Trans R Soc Lond B Biol Sci. 2006 Apr 29;361(1468):639-48.

*Self-reported reproductive outcomes among male and female 1991 Gulf War era US military Veterans.* Wells TS, Wang LZ, Spooner CN, Smith TC, Hiliopoulos KM, Kamens DR, Gray GC, Sato PA. Matern Child Health J. 2006 Nov;10(6):501-10.

*Gulf War Veterans and hemifacial microsomia.* Werler MM, Sheehan JE, Mitchell AA. Birth Defects Res A Clin Mol Teratol. 2005 Jan;73(1):50-2.

*Conception and pregnancy during the Persian Gulf War: the risk to women Veterans.* Araneta MR, Kamens DR, Zau AC, Gastañaga VM, Schlangen KM, Hiliopoulos KM, Gray GC. Ann Epidemiol. 2004 Feb;14(2):109-16.

*Prevalence of birth defects among infants of Gulf War Veterans in Arkansas, Arizona, California, Georgia, Hawaii, and Iowa, 1989-1993.* Araneta MR, Schlangen KM, Edmonds LD, Destiche DA, Merz RD, Hobbs CA, Flood TJ, Harris JA, Krishnamurti D, Gray GC. Birth Defects Res A Clin Mol Teratol. 2003 Apr;67(4):246-60.

*Pregnancy outcomes among U.S. Gulf War Veterans: a population-based survey of 30,000 Veterans.* Kang H, Magee C, Mahan C, Lee K, Murphy F, Jackson L, Matanoski G. Ann Epidemiol. 2001 Oct;11(7):504-11.

*Birth defects prevalence among infants of Persian Gulf War Veterans born in Hawaii, 1989-1993.* Araneta MR, Destiche DA, Schlangen KM, Merz RD, Forrester MB, Gray GC. Teratology. 2000 Oct;62(4):195-204.

*Goldenhar syndrome among infants born in military hospitals to Gulf War Veterans.* Araneta MR, Moore CA, Olney RS, Edmonds LD, Karcher JA, McDonough C, Hiliopoulos KM, Schlangen KM, Gray GC. Teratology. 1997 Oct;56(4):244-51.

**14. Do Gulf War Veterans report more pulmonary symptoms, or diagnoses, than persons in appropriate control groups?**

**15. Do Gulf War Veterans have a smaller baseline lung function in comparison to an appropriate control group? Do Gulf War Veterans have a greater degree of non-specific airway reactivity in comparison to an appropriate control group?**

While some studies have indicated that Gulf War Veterans are more likely to self-report pulmonary problems or to have more hospitalizations for diseases of the respiratory system (including asthma), other reports have found no increased prevalence of pulmonary symptoms or link between exposure to oil well fires and development of asthma.

*Late prevalence of respiratory symptoms and pulmonary function abnormalities in Gulf War I Veterans.* Karlinsky JB, Blanchard M, Alpern R, Eisen SA, Kang H, Murphy FM, Reda DJ. Arch Intern Med. 2004 Dec 13; 27;164(22):2488-91.

*Exposures to the Kuwait oil fires and their association with asthma and bronchitis among gulf war Veterans.* Lange JL, Schwartz DA, Doebbeling BN, Heller JM, Thorne PS. Environ Health Perspect. 2002 Nov;110(11):1141-6.

*A case-control study of asthma among U.S. Army Gulf War Veterans and modeled exposure to oil well fire smoke.* Cowan DN, Lange JL, Heller J, Kirkpatrick J, DeBakey S. Mil Med. 2002 Sep;167(9):777-82.

*Are Gulf War Veterans suffering war-related illnesses? Federal and civilian hospitalizations examined, June 1991 to December 1994.* Gray GC, Smith TC, Kang HK, Knoke JD. Am J Epidemiol. 2000 Jan 1;151(1):63-71.

*Variable extrathoracic airflow obstruction and chronic laryngotracheitis in Gulf War Veterans.* Das AK, Davanzo LD, Poiani GJ, Zazzali PG, Scardella AT, Warnock ML, Edelman NH. Chest. 1999 Jan;115(1):97-101.

## 4.2 Summary of Federal Funding of Gulf War Research 1994-2010

Fiscal Year	VA*	UTSW Contract**	DoD*	HHS*	FY Total
1994	\$ 1,157,879	\$ -	\$ 6,492,882	\$ -	\$ 7,650,761
1995	\$ 2,334,083	\$ -	\$ 10,973,000	\$ 2,514,762	\$ 15,821,845
1996	\$ 3,853,095	\$ -	\$ 11,905,214	\$ 1,616,755	\$ 17,375,064
1997	\$ 2,834,790	\$ -	\$ 28,880,536	\$ -	\$ 31,715,326
1998	\$ 4,722,820	\$ -	\$ 13,213,232	\$ 1,634,347	\$ 19,570,399
1999	\$ 9,006,155	\$ -	\$ 22,674,338	\$ 1,640,378	\$ 33,320,871
2000	\$ 12,020,519	\$ -	\$ 23,847,679	\$ 1,567,439	\$ 37,435,637
2001	\$ 8,576,675	\$ -	\$ 31,587,006	\$ 998,870	\$ 41,162,551
2002	\$ 4,512,676	\$ -	\$ 18,827,819	\$ 799,814	\$ 24,140,309
2003	\$ 5,746,467	\$ -	\$ 16,419,497	\$ 964,105	\$ 23,130,069
2004	\$ 7,644,560	\$ -	\$ 11,096,063	\$ 466,126	\$ 19,206,749
2005	\$ 9,484,679	\$ -	\$ 10,091,848	\$ 466,481	\$ 20,043,008
2006	\$ 12,942,066	\$ -	\$ 10,128,261	\$ 455,587	\$ 23,525,914
2007	\$ 6,977,767	\$ 15,000,000	\$ 3,417,570	\$ 441,974	\$ 25,837,311
2008	\$ 6,636,369	\$ 15,000,000	\$ 11,672,967	\$ 433,467	\$ 33,742,803
2009	\$ 8,685,533	\$ 6,972,481	\$ 3,145,000	\$ -	\$ 18,803,014
2010 §	\$ 7,714,416	\$ 2,288,755	\$ 3,145,000	\$ -	\$ 13,148,171
<b>Total 1994 - 2010</b>	<b>\$ 114,850,549</b>	<b>\$ 39,261,236</b>	<b>\$ 237,517,912</b>	<b>\$ 14,000,105</b>	<b>\$ 405,629,802</b>

\* Funds expended to support Gulf War research projects

\*\* Funds obligated for reimbursement to UTSW at completion of contracted work on individual task orders

§ Current estimate of VA, DoD and HHS funds allocated for GW research in FY 2010

The VA estimate for FY10 includes 40% of MRI imaging equipment upgrade at San Francisco for Gulf War research and use of unobligated FY2009 UTSW Contract funds for close-out costs of approved task orders and data transfer costs.

This estimate does not include expenditures from the VA Medical Care appropriation of \$3.7 million for the Veterans Equitable Resource Allocation (VERA) System to support funded Gulf War research projects. Historically, these costs have not been included in the FY expenditures reported above.

## 5.0 GULF WAR RESEARCH STRATEGIC OBJECTIVES 2011-2015

Seven Strategic Objectives have been identified for this plan.

1. Research to enable development of new Gulf War Case Definitions
2. Genetics/Genomics
3. Biomarkers
4. Symptomatic and Specific Treatments
5. Coordination/Communication between Partners and Researchers
6. Translation of Research into Practice
7. Animal Models

Five elements are presented for each strategic objective:

1. Objective
2. IOM Recommendations (quoted from IOM volume 8)
3. RACGWVI Recommendations (quoted from 2008 RACGWVI Report)
4. ORD Research or Activities
5. Research or Action Plans and Funding Mechanisms



## 5.1 CONDUCT RESEARCH TO ENABLE DEVELOPMENT OF NEW GULF WAR CASE DEFINITIONS

### 5.1.1 Objective

*Examine and evaluate the case definitions for Gulf War Illnesses. Develop new methodology and models that will inform the creation of new case definitions.*

More research on case definition for Gulf War Illnesses is clearly needed. There is very little published research on this topic, and the lack of consensus on a case definition continues to hamper research.

A case definition typically consists of a set of standard criteria for diagnosing a particular disease or health-related condition. Generally, exact clinical criteria are specified, often other limitations are imposed (e.g. time, location, etc). This matter becomes complicated in multisymptom illnesses, when symptoms in an individual may overlap. In Gulf War Veterans, examples include, but are not limited to, Chronic Fatigue Syndrome, Fibromyalgia, and Multiple Chemical Sensitivities.

The extra complexity involved in a case definition of Gulf War Illness that is a challenge to future research is illustrated by the following example. For fibromyalgia, the case definition requires both widespread pain (pain on both sides of the body, above and below the waist, and including axial skeletal pain) lasting for at least 3 months and pain (not just tenderness) in at least 11 of 18 tender point sites on palpation with an approximate force of 4 kg. Apparently, fibromyalgia is one of the conditions that applies to a subgroup of Gulf War Veterans. There is also a distinction between case definitions that are most useful for research and case definitions that are most useful for clinical care.

### 5.1.2 IOM Recommendations

The IOM (vol 8) has noted that: "No unique syndrome, unique illness, or unique symptom complex in deployed Gulf War Veterans has been found. Veterans of the Gulf War report higher rates of nearly all symptoms or sets of symptoms than their nondeployed counterparts; 29% of Veterans meet a case definition of "multisymptom illness," as compared with 16% of nondeployed Veterans."<sup>X19</sup>

### 5.1.3 RACGWVI Recommendations

Gulf War illness prevalence estimates vary with the specific case definition used.<sup>GW4</sup> The prevalence of Gulf War illness reported by different studies has varied with how Gulf War illness or "chronic multisymptom illness" (CMI) cases are defined. Because no specific Gulf War illness case definition has been widely accepted, the Committee reviewed prevalence estimates from all studies reporting rates of multisymptom illness, by any case definition, in both Gulf War Veterans and nondeployed Gulf War-era Veterans."<sup>GW25</sup>

### 5.1.4 ORD Research

ORD researchers, and other researchers as well, have developed research case definitions as needed for their various Gulf War research projects in a number of areas. VA and others have funded research on Gulf War case definition. This has included, for example, using factor analysis to derive syndromes and symptom-based case definition (Fukuda et al., 1998; Haley et al., 1997a; Haley et al., 1997b; Haley et al., 2002; Wolfe et al., 2002).



### 5.1.5 Research Plans and Funding Mechanisms

VA Researchers will develop new case definition methodologies and models. They will do this by using advances in health care information technology, data mining, bibliometric analysis, and other related areas to analyze:

- New symptom and health care data
- Medical and scientific literature related to Gulf War Illness,
- Results of past Gulf War Research Studies, and
- VA patient records of Gulf War Veterans
- Additional potential sources of information, such as Cochrane Reviews

The Gulf War Era Cohort and Blood Biorepository (CSP #585), which is under development, will recruit a cohort of Veterans from the Gulf War era to develop a research database that integrates epidemiological, survey, clinical, and self-reported environmental exposure data. Blood specimens will also be collected to establish a biorepository to enable a deeper level of research. Both users and non-users of VHA Healthcare will be recruited. Participants will also consent to be contacted about enrolling in other research projects. The data derived from this study will form the nucleus for developing improved case definitions of Gulf War Illnesses for both research and, ultimately, clinical purposes.

New developments in diagnostic capabilities, based on genetic, imaging and proteomic biomarkers for symptom-based conditions, will lead to more specific case definitions and better understanding of the underlying biologically based etiologies.

In FY2012, VA will begin using additional approaches to the case definition problem based on the HSRD Evidence-Based Synthesis Program. This will examine the conditions currently seen in Veterans that are associated with deployment in the Gulf War that can be used by an “expert working group” to develop case definitions and implement a strategy for validating them. These and other syntheses of evidence will further inform development of Gulf War case definitions.

The VA funding mechanism for new case definitions is likely to be through CSP 585 (and other projects to be developed). VA researchers are likely to also leverage funding from CDMRP and other sources.

## 5.2 GENETICS/GENOMICS

### 5.2.1 Objective

*Identify plausible hypotheses on the underlying causes and related pathways that might account for persistent symptoms in Gulf War Veterans.* Determine the genetic predisposition for each condition associated with Gulf War Illnesses. The goal of this initiative is to identify if there are genetic markers that predict and potentially verify a Gulf War Veteran’s response to hazardous environmental agents and that also guide the treatment options for that Veteran’s resulting health concerns.<sup>24</sup>

### 5.2.2 IOM Recommendations

The IOM has noted that “given the high prevalence of persistent symptoms and the steady advances in our understanding of genetics, molecular diagnostics, and imaging, it is now possible to plan and carry out

adequately powered studies to identify inherited genetic variants, molecular profiles of gene expression, other epigenetic markers (for example, modifications of DNA structure related to environmental exposures), specific viral exposures, signatures of immune activation, and brain changes identified by sensitive imaging measures that distinguish Gulf War Veterans who have persistent medical symptoms from healthy deployed or nondeployed Veterans.”<sup>X10</sup>

### 5.2.3 RACGWVI Recommendations

The RAQCGWVI noted that “a question often asked about Gulf War illness is why some Gulf War military personnel developed chronic symptoms during and after deployment, while others who served alongside them remained well. There is more than one possible reason for this. Genetic and other differences between individuals can dictate different reactions to a given exposure. Additionally, different individuals encountered varying doses and combinations of exposures in theater, over different durations. Identifying specific factors responsible for these differences would provide important insights into the biological nature of Gulf War illness, as well as its causes. It could also help prevent similar problems in future deployments.”<sup>GW250</sup>

### 5.2.4 ORD Research

Some examples of past research in genetics/genomics show the potential of these types of studies in Gulf War Research.

An ORD-funded study entitled “Patterns of Microarray Gene Expression in Gulf War Illness” examined 20,000 genes by microarray immediately before, immediately after and 4 hours following an exercise challenge. Ill Gulf War Veterans demonstrated impaired immune function, as demonstrated by decreased NK cytotoxicity and altered gene expression associated with NK cell function. Pro-inflammatory cytokines, T-cell ratios, and dysregulated mediators of the stress response (including salivary cortisol) were also altered in ill Gulf War Veterans compared to control subjects (Whistler T, et al, BMC Med Genomics. 2009 Mar 5;2:12).

“HIV-1 Genetic Determinants of Drug Resistance Development” was an ORD-funded retrospective cohort study which found that high sensitivity microarray genotyping predicted ART response better than standard sequencing. This enables VA clinicians to tailor therapy for their patients with the best ART regimens likely to suppress these resistant variants. (Lataillade M, Antivir Ther. 2007;12(4):563-70)

ORD researchers conducting genetic research in schizophrenia have found that functional polymorphisms in the core promoter of chromosome 15q14 locus of CHRNA 7 are associated with schizophrenia and with diminished inhibition of P50 auditory evoked responses. This finding is one of few demonstrations of a functional polymorphism in a gene associated with schizophrenia that directly affects a neuronal function. These results support the hypothesis of a familial neurobiological risk factor for the illness, as well as development of a drug to treat the condition. (Olincy A, Schizophr Res. 2010 Jun;119(1-3):175-82)

### 5.2.5 Research Plans and Funding Mechanisms

The most current and most important example of new ORD-funded research in this area is the Million Veteran Program (MVP). This is a platform upon which significant future Gulf War Research can be built.

The VA Office of Research and Development launched the Million Veteran Program (MVP) in early 2011. The MVP is an important partnership between VA and Veterans. The goal of MVP is to better understand how genes affect health and illness in order to improve health care for Veterans. MVP will establish one of the largest

databases of genetic and health information to be used for future studies that may lead to new ways of preventing and treating illnesses in Veterans and all Americans. The goal of MVP is to partner with Veterans receiving services in the VA health care system who volunteer to share their health information, as well as genetic material. Veterans who choose to be actively involved in this program will:

- Complete surveys about health and health-related behaviors;
- Provide a blood sample (containing DNA and other substances) that will be stored for future research;
- Complete an optional health assessment;
- Allow secure access to VA and VA-linked medical and health information, including past and future health records; and
- Allowing future contact for invitation to participate in additional research studies

MVP is a research program that will allow current Veterans to help transform health care, not only for themselves, but for future generations of Veterans.

VA researchers will continue adding data and specimens to develop the research capacity of the ORD biorepository studies:

- Gulf War Veterans Illnesses Central Nervous System Biorepository (ALS; CSP # 501) is a cooperative effort to collect high quality biological specimens linked to clinical information from consenting Veterans for use in biomedical research on GWVI. Initial efforts have focused on collection of central nervous system tissue (brain and spinal cord) from Veterans diagnosed with Amyotrophic Lateral Sclerosis (ALS), which has been reported to occur at higher rates in Gulf War Veterans.
- Gulf War Postmortem Biorepository (CSP #501A): This pilot project is an expansion of an existing project to develop a collection of high quality post mortem biological specimens (not limited to central nervous system) from Gulf War Veterans.
- Million Veteran Program (CSP #G002). This project is expected to enroll one million users of the VA Healthcare System, with representative sampling from all deployments including the 1990-1991 Gulf War. This new research project will become one of the largest databases of genetic and health information to be used for future studies that may lead to new ways of preventing and treating illnesses in Veterans
- Gulf War Era Cohort and Blood Biorepository (CSP #585). This large-scale longitudinal study, which is under development, will recruit a cohort of Veterans from the Gulf War era to develop a research database that integrates epidemiological, survey, clinical, and self-reported environmental exposure data. Blood specimens will also be collected to establish the biorepository to enable a deeper level of research. Both users and non-users of VHA Healthcare will be recruited. Participants will also consent to be contacted about enrolling in other research projects.

VA researchers will begin using the data and specimens in these repositories to:

- Determine the genetic predisposition for each condition that has been associated with Gulf War Illnesses.
  - Chronic Fatigue Syndrome

- Fibromyalgia
  - Chronic widespread pain
  - Multiple chemical sensitivities
  - Memory and Cognitive issues
  - Other illnesses commonly associated with deployment to the Gulf War
- Identify genetic markers that predict and potentially verify a Gulf War Veteran's response to hazardous environmental agents.
- Use genetic markers to guide the treatment options for the Gulf War Veteran's health concerns.

Most importantly, VA researchers will also have access to the cohort of Gulf War Veterans that are participating in the MVP as potential subjects for future research studies.

The VA funding mechanisms for Genetics/Genomics will be via RFAs and CSP. VA researchers are likely to also leverage funding from CDMRP and other sources.

## 5.3 BIOMARKERS

### 5.3.1 Objective

*Identify biomarkers/diagnostics that may be present in ill Gulf War Veterans.* Biomarkers typically mean any molecular or cellular events that can be identified as a link between a specific environmental exposure to a health outcome. Results from imaging technologies can also be considered biomarkers when they show particular alterations in a biological structure.

### 5.3.2 IOM Recommendations

"Many of these symptoms (Gulf War) are difficult to categorize as they have no known cause, no objective findings on clinical examination, no diagnostic biomarkers, no known tissue pathology, and no curative therapy. The inadequate basic understanding of the root cause of these symptoms highlights the limitations of current medical science and clinical practice. The (IOM) committee recognizes that symptoms that cannot be easily quantified are sometimes dismissed—incorrectly—as insignificant, and that they receive inadequate attention—and funding—by the medical and scientific establishment." <sup>xix</sup>

### 5.3.3 RACGWVI Recommendations

"Findings from studies of this type can therefore be affected by many of the problems described in relation to Gulf War illness research, that is, potential inaccuracies in identifying "exposed" vs. "unexposed" groups, the lack of useful biomarkers of exposure, and individual variability in specific exposures and vulnerability to those exposures. Given such limitations, it is important that this literature be considered broadly, taking into account patterns of associations across multiple studies and populations. Such studies can potentially provide insights into the pathophysiology of CFS and lay the groundwork for developing biomarkers and treatments." <sup>GW285</sup>

### 5.3.4 ORD Research

Some examples of ORD-funded research in this area are given below.

The study “Structural Magnetic Resonance Imaging in Gulf War-Era Veterans” found a significant association between higher levels of estimated sarin/cyclosarin exposure and both reduced white matter and increased right lateral ventricle and left lateral ventricle volumes. These findings suggested 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 (Heaton KJ, Palumbo CL, Proctor SP, Killiany RJ, Yurgelun-Todd DA, White RF, Neurotoxicology. 2007 Jul;28(4):761-9).

Tissue factor and Gulf War-associated chronic coagulopathies were studied in a group of 64 Gulf War Veterans and controls. Significant differences between the two groups were observed for three of eight coagulation parameters. The results of this study supported the hypothesis of coagulation system activation in GWI. This is a new potential biomarker for Gulf War Research (Bach and Slater, J Thrombosis and Haemostasis 2009; Volume 7, Supplement 2)

The study “Effects of Gulf War Illness on Brain Structure, Function and Metabolism: MRI/MRS at 4 Tesla” examined imaging biomarkers to determine whether US troops who may have been exposed to the organophosphate chemical warfare agents sarin (GB) and cyclosarin (GF) when a munitions dump at Khamisiyah, Iraq was destroyed during the Gulf War (GW) in 1991 have metabolic, structural, or functional changes in the basal ganglia and other regions of the brain, which are not accounted for by confounds such as post traumatic stress disorder (PTSD), depression, and/or alcoholism. The findings suggested that low-level exposure to GB/GF can have deleterious effects on brain structure and brain function more than decade later (Chao, Neurotoxicology. 2010 Sep;31(5):493-501)

In the ORD-funded study “Glucocorticoid Responsivity in Gulf War Veterans” hydrocortisone (Hcort) was administered to GW veterans with (PTSD+ n=12) and without (PTSD- n=8) chronic PTSD in a randomized, placebo-controlled, double-blind challenge. The PTSD+ group showed greater cortisol and ACTH suppression, reflecting greater peripheral glucocorticoid receptor (GR) responsiveness, and did not show an Hcort-induced decrement in delayed recall or retention. Positron-emission tomography demonstrated that while the two groups had comparable relative regional hippocampal [<sup>18</sup>F]FDG uptake at baseline, only the PTSD- group had an Hcort-associated decrease in hippocampal [<sup>18</sup>F]FDG uptake. The investigators concluded that the differences in brain metabolic responses between GW veterans with and without PTSD may reflect differences in peripheral and central GR responsiveness (Yehuda et al, Psychiatry Res. 2010 Nov 30;184(2):117-27.

### 5.3.5 Research Plans

VA Researchers will search for new biomarkers and validate them. These biomarkers include, but are not limited to:

- Functional magnetic resonance imaging (fMRI) biomarkers to understand central nervous system mechanisms of pain and fatigue in Veterans with Gulf War Illness.
- Immune response mediator biomarkers that are associated with chronic inflammation
- Hypothalamic-Pituitary-Adrenal axis biomarkers in chronic multisymptom illnesses

Promising recent VA pilot studies in biomarkers will be evaluated for expansion to larger studies in the future. As will be described in section 5.4.5, VA has the existing research infrastructure to conduct small pilot studies, and move the studies with the most promising results on to larger studies.

The VA funding mechanisms for Biomarkers will be via RFAs and CSP. VA researchers are likely to also leverage funding from CDMRP and other sources.

## 5.4 SYMPTOMATIC AND SPECIFIC TREATMENTS

### 5.4.1 Objective

*Develop symptomatic and specific treatments for Gulf War Illnesses.* Even if the mechanisms behind Gulf War Illnesses are not fully understood, it is possible to study and develop treatments that may improve a Veterans medical condition.

### 5.4.2 IOM Recommendations

The IOM noted that: “There is a dearth of organized clinical trials to examine potential treatments for the observed symptoms experienced by Gulf War Veterans. Aligned with the effort to improve care pathways for Gulf War illness sufferers, there should be a focused effort to consider the development of clinical trials informed by the best biological data related to the cause of Gulf War illness.”<sup>X10</sup>

### 5.4.3 RACGWVI Recommendations

“Gulf War illness is a serious condition that affects at least one fourth of the 697,000 U.S. Veterans who served in the 1990-1991 Gulf War. This complex of multiple concurrent symptoms typically includes persistent memory and concentration problems, chronic headaches, widespread pain, gastrointestinal problems, and other chronic abnormalities not explained by well-established diagnoses. No effective treatments have been identified for Gulf War illness and studies indicate that few Veterans have recovered over time.”<sup>GW1</sup>

### 5.4.4 ORD Research

Examples of past ORD research in this area are given below.

As part of an ORD-funded Career Development Award, a pilot clinical trial was conducted to determine whether nasal continuous positive airway pressure (CPAP) alleviates the symptoms of veterans with Gulf War illness (GWI) and sleep disordered breathing (SDB). Compared to the nine sham nasal CPAP recipients, the eight participants receiving therapeutic nasal CPAP experienced significant improvements in pain (34%), fatigue (38%), cognitive function (33%), sleep quality (41%), physical health (34%), and mental health (16%) Amin et al, Sleep Breath, 2010 Aug 19, [Epub ahead of print].

In a study of potential new treatments for IBS, the expression of glutamine synthetase and its complementary miRNA in blood microvesicles and gut tissues of IBS patients were studied. Data from 19 diarrhea-predominant IBS subjects and 10 controls supported the conclusion that GLUL regulates intestinal membrane permeability and miR-29a regulates both GLUL and intestinal membrane permeability. Targeting this signaling pathway could lead to a new therapeutic approach to the treatment of patients with IBS, especially because small molecules that mimic or inhibit miRNA-based mechanisms are readily available. (Zhou, Gut. 2010 Jun;59(6):775-84)



A randomized controlled multi-site clinical trial was developed through the Cooperative Studies Program to compare the effectiveness of cognitive behavioral therapy (CBT), exercise, and the combination of both for improving physical functioning and reducing the symptoms of Gulf War Veterans Illnesses (GWVI). The results suggested that CBT and/or exercise can provide modest relief for some of the symptoms of chronic multisymptom illnesses such as GWVI (Donta et al, JAMA. 2003; 289(11):1396-404).

The state of the cardiopulmonary system is important for planning treatments that involve exercise. A study of metabolic responses to maximal exercise in Gulf War Veterans with CFS was compared with a control group who did not have CFS. Compared with healthy controls, Veterans who report multiple medically unexplained symptoms and meet criteria for CFS do not show a decreased exercise capacity. Thus, it does not appear that the pathology of the GV's with CFS includes a deficiency with mobilizing the cardiopulmonary system for strenuous physical effort. (Nagelkirk et al Mil Med. 2003 Sep;168(9):750-5.)

#### 5.4.5 Research Plans and Funding Mechanisms

VA Researchers will investigate new treatments including, but not limited to:

- Resistance exercise training as a therapy for chronic pain – “Impact of Exercise Training on pain and Brain Function in Gulf War veterans” is a five-year study to evaluate resistance exercise training (RET) as a therapy for chronic musculoskeletal pain and associated symptoms in Gulf War Veterans. The study will evaluate the influence of RET on total physical activity, pain sensitivity and regulation, and the structure of brain white-matter tracts.
- Mindfulness-Based Stress Reduction treatment for fatigue, pain, and cognitive function. “A randomized controlled trial of a mindfulness based intervention for Gulf War Syndrome” is a 2-year pilot study that will include randomized, controlled, eight-week trials of an intervention known as “mindfulness-based stress reduction” (MSBR), compared with usual care. Assessments of Veterans will include symptom-based measures of pain, fatigue, and cognitive and physical function as well as objective measures of attention, concentration and memory. MSBR has been shown to improve fatigue, pain and cognitive function (attention, concentration and memory) in other chronic multisymptom illnesses, such as chronic fatigue syndrome and fibromyalgia.
- “Diarrhea-Predominant Irritable Bowel Syndrome in Persian Gulf Veterans” will determine if small bowel bacterial overgrowth (SBBO) is the cause of diarrhea-predominant symptoms in ill GW Veterans and if treatment with the antibiotic rifaximin to eradicate SBBO leads to improvement of symptom
- Evaluating existing treatments for other conditions that could be applied to Gulf War Illnesses.

VA has an established research infrastructure to support research projects of various sizes and complexity. Current pilot studies will be evaluated for expansion to larger trials. For the Gulf War Research Portfolio, ORD will:

- Expand the number of “small projects” in the area of new treatments that could lead to larger studies (Pilot Projects and single-site pilot clinical trials).
- Based on findings consider replicating promising “small projects” with expanded studies at 2 or three (Cooperative Clinical Trial Awards).

- Also based on findings, transition the most promising treatment studies to a national multi-site (10 or more sites) clinical trial through the Cooperative Studies Program

The VA funding mechanisms for Symptomatic and Specific Treatments will be initially studied through RFAs and CDMRP, followed by CSP development of multisite trials.

## **5.5 IMPROVE COORDINATION AND COMMUNICATION WITH FEDERAL PARTNERS, RESEARCHERS, AND THE PRIVATE SECTOR**

### **5.5.1 Objective**

*The purpose of this objective is to improve coordination and cooperation with all partners involved in Gulf War Research.* This would include

- Gulf War advisory boards, committees, task forces, etc.
- Veteran's Service Organizations
- Government research administrators (both VA and DoD)
- Gulf War researchers (both federally funded and non-federally funded)

### **5.5.2. Inter-Governmental Coordination Efforts**

Within VA, two organizations, ORD and OPH, are involved in Gulf War Research. ORD and OPH internally coordinate and share information on Gulf War Research. In early 2011, ORD and OPH initiated formalized quarterly meetings of senior staff and, as appropriate, scientific program managers and VA investigators.

#### **5.5.2.1 Office of Research and Development (ORD)**

The Office of Research and Development (ORD) supports the discovery of new knowledge, by developing VA researchers and health care leaders, and creating innovations that advance health care for our Veterans and the nation. ORD funds research and set research priorities in four areas, biomedical, clinical, rehabilitation, and health services research.

ORD staff participate in regularly scheduled meetings of the RACGWVI, the Gulf War Steering Committee, and the Gulf War Veterans' Illnesses Task Force. These lines of communication and coordination are valuable avenues of information sharing.

#### **5.5.2.2 Office of Public Health (OPH).**

The Office of Public Health (OPH) performs epidemiological research and large scale surveillance studies. OPH coordinates and supports Institute of Medicine Studies that consolidate current knowledge of the Gulf War and other deployment health conditions.



ORD and OPH complement one another in that OPH performs high level surveillance studies (e.g., prevalence, mortality), while ORD performs basic scientific and applied medical research. Results of OPH studies support ORD's research agenda (e.g., increased prevalence of a particular condition in a certain Veteran population could be an indicator that a certain research project may be needed for further study to seek a mechanism and a treatment).

#### ***5.5.2.3 DOD's Congressionally Directed Medical Research Program (CDMRP)***

Outside of VA, ORD coordinates with DOD's Congressionally Directed Medical Research Program (CDMRP), specifically its Gulf War Illness Research Program. In a number of cases, VA investigators have successfully competed for research funding from CDMRP.

CDMRP views Gulf War Illness (GWI) as characterized by persistent symptoms such as chronic headache, widespread pain, cognitive difficulties, unexplained fatigue, gastrointestinal problems, respiratory symptoms, and other abnormalities that are not explained by traditional medical or psychiatric diagnoses. CDMRP estimates that this complex set of chronic symptoms may affect as many as 200,000 Veterans of the 1990-1991 Gulf War, of the over 700,000 deployed to that region. The CDMRP GWIRP focuses its funding on projects that have relate to GWI.

The Vision for the CDMRP GWIRP is to "Improve the health and lives of Veterans who have Gulf War Illness", and the mission is to: "fund innovative Gulf War Illness research to identify effective treatments, improve definition and diagnosis, and better understand pathobiology and symptoms."

ORD and the Gulf War Illness Research program (GWIRP) within CDMRP already maintain several levels of coordination:

- 1) The VA Gulf War Program Manager is invited to present the VA Gulf War research portfolio as part of the GWIRP vision setting meeting each year. The VA GW research portfolio and upcoming requests for applications (RFAs) are discussed at this time. This allows both agencies to coordinate their research priorities.
- 2) The VA GW research portfolio and the GWIRP research portfolio are presented and discussed at one or more of the 3 annual meetings of the VA Research Advisory Committee on Gulf War Veterans' Illnesses (RACGWVI). This allows the RACGWVI to be aware of the activities within each agency's GW research program so that appropriate recommendations may be formulated.
- 3) Representatives from the GWIRP are invited to present at VA Gulf War Steering Committee meetings so that the committee is aware of the scope and potential overlap between the VA and DoD programs.

#### ***5.5.2.4 Deployment Health Working Group (DHWG)***

The DHWG is an interagency working group co-chaired by VA and DoD that meets monthly (successor to the original PGVCB). The DHWG reports to VA/DoD joint committees. The DHWG is composed of staff from OPH, ORD, and Veterans Benefits Administration (VBA). The working group shares information on deployment health in all areas, environmental exposures, DoD/VA data sharing, surveillance, surveys, research, and other topics as needed.

#### **5.5.2.5 Veterans Service Organizations**

ORD also provides briefings to a number of Veterans Service Organizations on at least an annual basis (sometimes more frequently when requested). These lines of communication and coordination are valuable avenues of information sharing.

#### **5.5.3 ORD Coordination Efforts Among Researchers**

ORD also has a responsibility to not only monitor research that is being funded, but also to bring researchers together, when appropriate and encourage coordination and collaboration.

Collexis® is a leading developer of semantic search and knowledge discovery software. It has developed applications that range from search tools for websites to highly sophisticated discovery applications. These applications allow the user to identify and search for documents, experts, trends, or new discoveries. Using the Collexis Knowledge Engine, VA will better coordinate research, index, categorize, trend and match information inside ORD's own internal data for discovery. Collexis will be used to better understand ORD's research history and capabilities by aggregating the "conceptual fingerprints" of existing published papers. By using historic publishing and citation data to expose unique relationships among researchers and institutions, Collexis can provide VA Program Managers with transparency while researchers can use it to identify others with whom to collaborate.

#### **5.5.4 Research and Action Plans**

The *VA Research and Development Strategic Plan: 2009-2014* stresses the need for a communication portal to improve communication among VA researchers.<sup>4,8</sup>

- VA will improve communication between Gulf War Researchers from both VA and DoD by using new online technologies such as Sharepoint for researcher interaction, and Collexis for analysis of research projects to identify researchers that are working in similar areas and can benefit by interacting (two examples for illustrative purposes only).
- VA will convene a meeting of Gulf War Researchers in FY 2012 to improve sharing of research results and research strategies between researchers.
- Developing a secure method specifically for Gulf War researchers to share data when appropriate.
- VA will also provide strong leadership and organizational skills to this plan in the form of the new full-time Director of the Gulf War Research Program within ORD.
- Continue and enhance interactions and collaborations noted above

## **5.6 TRANSLATE RESEARCH FINDINGS TO PRACTICE**

### 5.6.1 Objective

*Translate research findings into practice as rapidly as possible.* Without exception, this is a problem in every field of medical, scientific and engineering research. It is important to accomplish this translation, so that the benefits of research will be experienced by individuals the research was intended to help.

### 5.6.2 Research and Activities

Once a promising technology or treatment has been selected to go forward, it continues to be subject to an adoption process that varies widely. One method is to set up specialty centers, where a particular treatment or treatment program is/are available. Another method is by developing educational programs for both Veterans and health care providers in the VA.

The War Related Illness and Injury Study Centers (WRIISC), under the direction of OPH, offer a number of special clinical programs for Veterans who have post-deployment health concerns. These programs focus on difficult to diagnose or medically unexplained symptoms and military environmental exposure concerns. These Centers are at the forefront of translating research into practice in the VA. The Centers offer a National Referral Program which provides comprehensive multidisciplinary health evaluations. The WRIISC also perform primary clinical research, provide exposure assessment clinics, and tele-health services.

The War Related Illness and Injury Study Centers (WRIISC) are also an educational resource for combat Veterans, their family members and loved ones, and Veteran health care providers. Their educational programs provide information on topics ranging from environmental exposures and deployment health conditions, to self management techniques for chronic health concerns.

VA is also committed to Clinician Education and Training. VA is developing accessible, flexible and user friendly training regarding health aspects of the Gulf War including Gulf War Veterans' Illnesses to educate primary care physicians, compensation and pension examiners, environmental health clinicians, mental health professionals and social workers about the health effects, including gender specific health effects of service in the 1990 – 1991 Gulf War.

OPH programs, the Environmental Agents Service, and War-Related Injury and Illness Study Centers (WRIISCs) are coordinating with Patient Care Services, the Office of Academic Affairs, Veterans Integrated Service Networks, and VA Medical Centers to improve training on the unique exposure concerns of 1990 – 1991 Gulf War Veterans as well as returning OEF/OIF Veterans, and provide educational and clinical tools for evaluation of exposure risk and the health outcomes relevant to these risks.

### 5.6.3 Research and Action Plans - Funding Mechanisms

When Gulf War research results show a successful treatment, they will be considered for translation to clinical practice. Moving treatments that have been shown to be successful in the research laboratory to clinical practice require different combinations of the following:

- Establish an evidence base through large well-designed research studies that can be published in leading journals.

- The VA Quality Enhancement Research Initiative (QUERI) is aimed at improving the quality of healthcare for Veterans. QUERI contributes to this effort by implementing research findings and innovations into routine clinical practice. As treatments and technologies emerge from research and are ready to be translated, appropriate knowledge from QUERI will be used to facilitate the transfer.
- Continuing education of VA health care providers is important because of the constant advances that are being made in research and the need to incorporate recent advances.
- ORD will coordinate with the War-Related Injury and Illness Centers and disseminate research findings to these three centers.
- ORD will encourage Gulf War Researchers to apply for the career development awards available through VA to build research capacity.

The VA funding mechanisms for translation of research results into practice will be initial studies through RFAs and CDMRP, followed by CSP development of multisite trials efficacy trials. WRIISC and QUERI mechanisms will be ultimately used for implementation studies.

## 5.7 ANIMAL MODELS

### 5.7.1 Objective

*Develop improved animal models to examine the mechanisms for Gulf War Illnesses and study potential treatments.* Animal models can be used judiciously to study certain aspects of Gulf War Illnesses. While there may not be a “perfect” animal model of Gulf War Illnesses, it is likely that some useful knowledge can be gained by using animal models, particularly, but not limited to, exposure to toxic substances.

### 5.7.2 IOM Recommendations

The IOM Gulf War Report (vol 8) noted that: “Because the committee was not attempting to link health outcomes to exposures other than deployment to the Persian Gulf theater, for which there is no known animal model, it did not review toxicologic, animal, or experimental studies comprehensively; however, it did evaluate the key epidemiologic and animal studies cited in the RACGWVI report (see Appendix A).”<sup>x3</sup> The IOM acknowledged, however, that animal studies might prove helpful in providing biologic understanding of many of the effects seen in humans from specific exposures, such as pesticides, solvents, and nerve agents, which have been reported by troops deployed in the Gulf War.<sup>x25</sup>

### 5.7.3 RACGWVI Recommendations

Most studies that evaluate biological effects of hazardous exposures are done in animals, for ethical reasons. In recent years, a large number of animal studies have identified biological effects of Gulf War exposures and combinations of exposures that were previously unknown.

### 5.7.4 ORD Research

One example of past research in animal models is given below.

ALS is a disease of concern to Gulf War Veterans. A transgenic mouse model of ALS was used to study the effect of high and moderate levels of exercise on body weight, motor performance, and motor neuron counts in the ventral horn of spinal cords. Moderate exercise delayed the onset of motor deficit by over a week. Motor neuron density in the lumbar cord was significantly higher in the moderate exercise group compared to the sedentary group at 95 days of age. These results show the beneficial effects of moderate exercise on the preservation of motor performance that correlates with higher motor neuron density in the ventral horn of the lumbar spinal cord in mice. (Carreras et al, Brain Res. 2010 February 8; 1313: 192–201)

#### **5.7.5 Research Plans and Funding Mechanisms**

VA Researchers will develop and use animal models that allow investigation of the nature of Gulf War Illnesses with respect to mechanisms and the ability to test potential treatments. Current pilot studies will be evaluated for expansion to larger trials. These animal models have historically involved exposure to toxic substances that were present in the Gulf War; however other “non-exposure” studies will also be conducted (such as the sleep example below). Examples include but are not limited to:

- Direct delivery of neurotoxins to brain by intranasal route, which differs from traditional systemic or transdermal approaches, and merits future research. This technique allows lower doses of the neurotoxin to be delivered.
- Long term changes in behavior of hippocampal neural stem cells after exposure to chemicals such as DEET, Permethrin, and pyridostigmine bromide.
- Studies of sleep neurobiology and neural circuitry responsible for the transition between sleep and wakefulness with a view toward identifying new therapies for sleep disturbances.
- Memory and Mood Enhancing Therapies for Gulf War Illness, which attempt to develop new therapies for Gulf War Illnesses

The VA funding mechanism for animal models will be RFAs. VA researchers are also likely to leverage other funding mechanisms as well.

## 6.0 CONCLUSIONS

The first "Working Plan" for Research on Persian Gulf War Veterans' Illnesses was published in 1995-96. The advances that have been made in medical and scientific research since this first Gulf War "Working Plan" was put forward include mapping the human genome, advances in medical imaging, and advances in medical informatics and electronic health information, to name but three technologies that were not available in 1995-96.

Examples of advances made by VA researchers have included: imaging studies that have shown alterations in brain structure in Gulf War Veterans exposed to sarin/cyclosarin; efficacy of Continuous Positive Airway Pressure (CPAP) to relieve some symptoms of Gulf War Illness; and Mindfulness-Based Stress Reduction treatment for fatigue, pain, and cognitive function.

The leadership of VA Office of Research and Development, in preparing this Strategic Plan for Gulf War Research, has recognized that these and other substantial advances have been made. The results of the ongoing Gulf War research programs that were initiated after the Gulf War have also made important progress. Collectively, these suggest new and innovative approaches to future Gulf War research.

The overall goal of the *Gulf War Research Strategic Plan 2011-2015* is to improve the health and well-being of Gulf War Veterans and to utilize emerging knowledge to prevent similar war-related illnesses in the future.

Progress has been made in Gulf War Research, yet much work remains to be done. This *Gulf War Research Strategic Plan 2011-2015* has been formulated to make clearer the way forward in research. The *Gulf War Research Strategic Plan 2011-2015* will be reviewed annually by the Gulf War Steering Committee, and updated as needed.





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