Research Advisory Committee on Gulf War Veterans' Illnesses

January 7-8, 2014 Committee Meeting Minutes

Department of Veterans' Affairs
Washington, DC

Research Advisory Committee on Gulf War Veterans' Illnesses
Boston University School of Public Health
715 Albany Street, T4W, Boston, MA 02118
Phone: 617-414-1392, Fax: 617-638-4857

I hereby certify the following minutes as being an accurate record of what transpired at the January 7-8, 2014 meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses.

/signed/
James H. Binns
Chairman
Research Advisory Committee on Gulf War Veterans' Illnesses

Table of Contents

Appendix A

Appendix B

Appendix C

Attendance Record

Members of the Committee
James Binns, Chairman
Roberta White, Scientific Director
Joel Graves
James Bunker
Nancy Klimas
Fiona Crawford
James O'Callaghan
Lea Steele
Beatrice Golomb

Committee Staff
Kimberly Sullivan, Associate Scientific Director
Brittany Sutton

Designated Federal Officer
Victor Kalasinsky

Guest Speakers
Melissa Forsythe
Gordon Broderick

VA Office of Research and Development
Robert Jaeger
Victor Kalasinsky
Timothy O'Leary

VA Office of Public Health
Victoria Davey

VA Office of Public and Intergovernmental Affairs
Robert Jesse, Principal Deputy Under Secretary of Health
Madhulika Agarwal, Deputy Under Secretary for Health Policy and Services

VA Office of General Counsel
Jonathan Gurland
Jessica Tanner

Abbreviations

ACTH – Adrenocorticotropic Hormone
CDMRP – Congressionally Directed Medical Research Program
CFS – Chronic Fatigue Syndrome
CMI – Chronic Multisymptom Illness
CSP – Cooperative Studies Program
DFO – Designated Federal Office
DoD – Department of Defense
EEG – Electroencephalography
FACA – Federal Advisory Committee Act
FOIA – Freedom of Information Act
FY – Fiscal Year
FM – Fibromyalgia
GW – Gulf War
GWI – Gulf War Illness
HPA – Hypothalamic-pituitary adrenal
HPG – Hypothalamic-pituitary gonadal
HPT – Hypothalamic-pituitary thyroid
IBS – Irritable Bowel Syndrome
IL-1 – Interleukin-1
IL-10 – Interleukin-10
IL-15 – Interleukin-15
MS – Multiple Sclerosis
NF-kB – Nuclear factor kappa beta
NSU – Nova Southeastern University
OEF – Operation Enduring Freedom
OIF – Operation Iraqi Freedom
OPH – Department of Veterans Affairs Office of Public Health
ORD – Department of Veterans Affairs Office of Research and Development
PB – Pyridostigmine Bromide
PCP – Primary care physician
PTSD – Post-Traumatic Stress Disorder
RAC – Research Advisory Committee on Gulf War Veterans' Illnesses
R&D – Research & Development
RFA – Request for Application
SGE – Special Government Employee
VA – Department of Veterans Affairs
VAMC – Department of Veterans Affairs Medical Center
VA-ORD – Department of Veterans Affairs Office of Research and Development
VO2 – Vanadium oxide 2
WRIISC – War Related Illness and Injury Study Center

Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses
January 7-8, 2014

Department of Veteran Affairs, 810 Vermont Avenue, Room 230, Washington, DC

Agenda
Tuesday, January 7, 2014

8:00 – 8:25	**Informal gathering, coffee**	
8:25 – 8:30	**Welcome, introductory remarks**	**Mr. Jim Binns, Chairman** **Res Adv Cmte Gulf War Illnesses**
8:30 – 9:15	**Gender differences in Gulf War Illness**	**Dr. Nancy Klimas** **Miami VA Medical Center**
9:15 – 10:00	**Identifying therapeutic strategies in Gulf War Illness with systems biology**	**Dr. Gordon Broderick** **Nova Southeastern University**
10:00 –10:15	**Break**	
10:15 -11:00	**CDMRP Gulf War Illness Research Program update**	**Dr. Melissa Forsythe** **Congressionally Directed Medical Research Program**
11:00 – 12:00	**Update of VA ORD Gulf War research Portfolio**	**Dr. Victor Kalasinsky** **Dr. Robert Jaeger** **VA Office of Research and development**
12:00 - 1:00	**Lunch**	
1:00 – 1:45	**Ethics and Federal Advisory Committee Training**	**Mr. Jonathan Gurland** **Ms. Jessica Tanner** **VA Office of General Counsel**
1:45 - 3:00	**Committee Discussion: 2013 Committee Report**	**Mr. Jim Binns, Chairman** **Dr. Roberta White, Scientific Director** **Res. Adv Cmte Gulf War Illnesses**
3:00 – 3:15	**Break**	
3:15 – 4:30	**Committee Discussion: 2013 Committee Report**	**Mr. Jim Binns, Chairman** **Dr. Roberta White, Scientific Director** **Res. Adv Cmte Gulf War Illnesses**
4:30 – 5:00	**Public comment**	

Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses
January 7-8, 2014

Department of Veteran Affairs, 810 Vermont Avenue, Room 230, Washington, DC

Agenda
Wednesday January 8, 2014

8:00 – 8:30	**Informal gathering, coffee**	
8:30 – 10:00	**Committee Discussion:** **2013 Committee Report**	**Mr. Jim Binns, Chairman** **Dr. Roberta White, Scientific Director** **Res. Adv Cmte Gulf War Illnesses**
10:00 – 10:15	**Break**	
10:15 - 12:00	**Committee Discussion**	**Mr. Jim Binns, Chairman** **Dr. Roberta White, Scientific Director** **Dr. Kimberly Sullivan, Assoc. Scientific Dir.** **Res Adv Cmte Gulf War Illnesses**
12:00 – 12:30	**Public comment**	
12:30	**Adjourn**	

DAY 1

The January 7th, 2014 meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses (hereinafter referred to as the Committee) was held in the Sonny Montgomery Room (Room 230) at the U.S. Department of Veterans Affairs Central Office, 810 Vermont Avenue, NW Washington DC.

Welcome

Mr. James Binns, Committee Chair

Chairman Binns called the meeting to order at 8:30 AM on Tuesday, January 7th, 2014. He thanked the guest speakers and Department of Veterans Affairs (VA) staff including Dr. Robert Jesse and Dr. Agerwal for attending the meeting. He thanked the Gulf War (GW) veterans who traveled from around the country to be present at the meeting. He also welcomed the newly appointed Committee members.

Introductory Remarks

Dr. Roberta Jesse, VA Principal Deputy Under Secretary for Health

Dr. Jesse thanked the members of the Committee and all others present at the meeting. He expressed optimism about the Gulf War research conducted in recent years, and his optimism for future leveraging of results by the Committee.

Dr. Jesse introduced the newly appointed members of the Committee including Gulf War veteran representatives Mr. Jim Bunker and Dr. Stephen Ondra (not present at meeting) and the newly appointed scientific representatives on the Committee included Dr. Fiona Crawford, Dr. Nancy Klimas, and Dr. Martin Philbert (not present at meeting).

Introductory Remarks

Mr. James Binns, Committee Chair

Chairman Binns provided a brief history of the Committee to provide some background for the new Committee members present. He explained that the Committee had been in existence for 12 years. He explained that over the years, the Committee had operated under a charter that directed it to measure the success of government research efforts in terms of whether they improved the health of Gulf War veterans. VA had made very limited progress, and there was still a clear need for the Committee to continue. He explained that at the end of 2008 and the beginning of 2009 two things happened that sparked some positive change. The Committee released a major report, and former Col. John Gingrich, a GW veteran, came in as the new VA chief of staff to the Secretary of Veterans Affairs. These developments were followed by three years of positive change, which was also strengthened by a 2010 Institute of Medicine (IOM) report that confirmed most of the findings published in the Committee's 2008 report. Positive changes

included improvements in the training program for VA doctors caring for Gulf War veterans, a letter sent to VA benefits offices expanding the understanding of undiagnosed illnesses, a VA task force created to address all aspects of Gulf War illness, and a Strategic Research Plan prepared by working groups of VA staff members, Committee members and other outside advisors from VA's National Research Advisory Council.

Abruptly in early 2012, this progress stopped and reversed. Edits were unilaterally made to the strategic plan by VA staff, reasserting outdated views of GWI. An Institute of Medicine treatment study ordered by Congress to be done by doctors who treat Gulf War veterans was transformed by VA into a literature review of largely psychiatric treatments by doctors with no Gulf War veteran patients. In June 2012, the Committee objected to these and other similar actions, which continued the pattern followed by VA since the war, except for the 2009-2011 progress.

Chairman Binns hoped that progress could be renewed. Finding treatments for Gulf War illness is not easy science. It is unconscionable that the greatest obstacle researcher's face is the renewed effort of government staff to shape research to mask the problem rather than to solve it.

Dr. Kimberly Sullivan, the associate scientific director, introduced the first scientific presenter Dr. Nancy Klimas.

Gender differences in Gulf War Illness

Dr. Nancy Klimas, Miami VA Medical Center

Dr. Nancy Klimas, a physician at the Institute for Neuro-Immune Medicine of the Nova Southeastern University (NSU) College of Osteopathic Medicine and the Miami VA Medical Center (VAMC) discussed how she and her colleagues approach complex illnesses including GWI, how they assess them and how they treat them. For Dr. Klimas' presentation slides, please refer to **Appendix A – Presentation 1**.

Dr. Klimas provided the Committee with a presentation on the work that she has done with the Institute for Neuro-Immune Medicine at Nova Southeastern University (NSU) College of Osteopathic Medicine. She explained that more than 25% of veterans returned from the Gulf War with a chronic often disabling multisymptom illness. She also described Chronic Fatigue Syndrome (CFS). She stated that between 800,000 and 2.5 million Americans are affected by it, and it is five times more common in women. Dr. Klimas works with the NSU Institute for Neuro-Immune Medicine clinical and research teams in partnership with the Miami VAMC. The institute considers its work focus to be integrative medicine with a research backbone.

Dr. Klimas then described the symptoms of Gulf War Illness and how they differ from Chronic Fatigue Syndrome. Autonomic dysfunction in GWI includes neurally mediated hypotension, orthostatic hypotension, parasympathetic dysfunction, and sympathetic over activation. With regard to the autonomic nervous system, symptoms included but were not limited to decreased

cerebral perfusion at rest and after physostigmine challenge in GWI and heart rate variability as a predictor of CFS.

These observations gave way to implications for treatment. Dr. Klimas noted that on a good day, a GWI patient is a liter short on blood volume. Interventions may include: filling the space by increasing plasma volume, regulating the pump using beta blockers, compress the space using alpha 1 agonists, and reconditioning.

Dr. Klimas then discussed immune modulation in GWI. Evidence suggests that there are two targets, the first being reducing inflammation (particularly neuroinflammation), and the second being enhancing antiviral function (particularly cytotoxic function). With regard to reducing inflammation, Dr. Klimas discussed two options including Omega 3 in high dosing ranges and low dose naltrexone. The second option would include reducing exposure to known immune stimulants such as allergens. With regard to improving antiviral function, supplements with placebo control data in related illnesses that could be considered include inosine or isoprinosine, mushroom extracts, and Equilibrant.

Neuroendocrine interventions were then discussed as was the importance of good sleep hygiene for health. With regard to pain and sleep, Dr. Klimas noted that the clinical dogma states that restorative sleep is the key to health improvement. She explained that trials in fatigue management report pain improvement with sleep restoration.

In fibromyalgia (FM) patients and the FM subset of GWI, there are three pain medications and one pipeline sleep medication that Dr. Klimas suggested may be helpful. These included Pregabalin (Lyrica), Duloxetine (Cymbalta), and Milnacipran (Savella). It was noted that opiates and alcohol increase neuroinflammation and reinforce central pain processing up-regulation and should be avoided.

Nutritional interventions have been explored as well. Oxidative stress studies have suggested interventions such as glutathione, N-acytylcysteine, alpha lipoic acid, and NADH. Vitamin studies have suggested B vitamins, Vitamin C, magnesium, sodium, zinc, l-tryptophan, L carnitine, co-Q10, and essential fatty acids. It was worth noting that CoQ10 is the only medication with favorable GWI data in placebo control studies.

Dr. Klimas then discussed reconditioning and cognitive behavioral therapy (CBT). Poor orthostatic resilience leads to substantial challenges to usual reconditioning programs. There are some important components to include in these programs. They should concentrate on muscle bulking exercises and in increasing metabolic rate with weight training using light weights. When possible, obtain the VO2 max and use a pulse meter to keep the efforts below the aerobic threshold.

Dr. Klimas concluded that the neuroendocrine, immune, and central nervous system are linked, and cannot be considered separately. Viewing the illness as a disorder that requires homeostasis resetting will have important treatment implications.

Dr. Klimas then spoke about practical implications based upon the Institute's work thus far. Medications directed at reducing inflammation and neuroinflammation that include low dose naltrexone, high dose omega 3 fatty acids, and antioxidants are an important study focus. Repeated stress responses can help to potentiate GWI, and buffering stress makes a difference. Exercise intolerance is very real and exercising to the VO2 max will cause relapse in these patients. Working within an "energy envelope" can be helpful. It is important to optimize cellular energy and repair mechanisms, and to measure and optimize vitamin D and B12; keep patients working on improving nutrition and judicious use of supplements.

Dr. Klimas then discussed primary care, GWI, and the VA resources available. She stated that without an "expert" GWI clinic, care is still accessible in the VA. The primary care physician can help to manage endocrines, pain, and sleep. A sleep clinic will be important to rule out apnea and assist in restorative sleep. Rehabilitation and physical therapy, chiropractics, and acupuncture can all be used to help with pain management and to develop a rehabilitation program. A cardiology focus may be needed for autonomic dysfunction. An endocrine focus is important for complex endocrine management, and for metabolic disorder.

The final part of Dr. Klimas' presentation was about whether men and women are different in regard to GWI, and whether or not it matters. While men with GWI have been extensively studied, there is considerably less knowledge about women veterans with GWI due to the limited numbers of female veterans in research studies. Large survey studies, particularly those that have evaluated fertility and risk of birth defects have revealed inconclusive results per IOM reports. A few studies that have assessed gender differences have revealed that women appear to present with increased autonomic abnormalities, as measured by heart rate variability, and some differences in symptom cluster as compared to their male counterparts.

There are implications for women in neuroendocrine, autonomic, and immune interactions in GWI and CFS. Previous research efforts have revealed that endocrine, autonomic and immune abnormalities were more prevalent in GW deployed veterans as compared to healthy controls. These systems co-regulate each other, and dysregulation in one system will undoubtedly impact the others.

Dr. Klimas discussed discordant models with regard to male and female predominance. In the Institute's modeling studies, the male GWI model showed up regulation of signaling pathways, and traffic through the sex hormone nodes; these impact immune and cellular pathways. In the predominantly female CFS model the opposite was found. Signaling was reduced or shut down, and there was a down regulation of signaling and metabolic pathways, again trafficking through sex hormone nodes in a clearly defined regulatory network. Hypothalamic-pituitary-adrenal

(HPA), Hypothalamic-pituitary-thyroid (HPT) and Hypothalamic-pituitary-gonadal (HPG) axis and immune regulation was then discussed. HPA influences immune function in well recognized ways, such as: cortisol regulation, thyroid mediated metabolic dysfunction as well as through regulatory networks, autonomic and immune function.

She also stated that her study results suggested that GWI and CFS are mediated differently, and the mediators of relapse and persistence in women with GWI are different than those in men. Currently this is in cytokine networks only; additional GWI female subjects are necessary to allow adequate power for the genomic analysis and networking analyses necessary to model and locate therapeutic targets.

Following the presentation, Dr. Sullivan asked whether Interleuken-10 (IL-10) was reduced in women in Dr. Klimas' studies, and whether it was anti-inflammatory. Dr. Klimas replied that IL-10 was anti-inflammatory, but was down in both men and women, which was a commonality between both. Dr. Klimas noted that the Committee should remember that these were just cytokine analyses, they are not genomics yet.

Dr. Jesse asked whether there was a systemized protocol to identify core issues for a given patient who was newly presenting at the clinic. Dr. Klimas replied that this protocol has developed over the years in her clinic. She stated that every patient presents uniquely, because while they may have matching symptoms, they are also different body types with different lifestyles that influence their health.

Dr. Jesse also asked whether the clinical approach she takes is matured enough to apply in primary care at other VA facilities. Dr. Klimas stated that she does believe this approach is ready for deployment across VA facilities.

Dr. O'Callaghan asked whether there are any pain clinics within the VA that have data to inform animal studies, as there are very few animal studies that deal with pain. She said that she wasn't sure that the pain clinics are the best for a patient with Gulf War illness. They are fast-paced clinics using opiates and pain blocks primarily for treatment and that may not be the best choice for treating Gulf War veterans.

Mr. Bunker asked about the limited time that primary care physicians claim to have for a Gulf War veteran presenting with symptoms. Dr. Klimas recommended that given their patient case load, primary care physicians (PCP) often have only about 15 minutes of time to spend with each patient. She recommended that veterans book appointments back to back, to block enough time with the physician.

CDMRP Gulf War Illness Research Program Update

Dr. Melissa Forsythe, Department of Defense Congressionally Directed Medical Research Programs

Dr. Forsythe began her presentation by thanking the Committee for the invitation to speak. She noted that the Congressionally Directed Medical Research Program (CDMRP) had been very busy in recent months, highlighting the Gulf War Illness research program (GWIRP). Dr. Forsythe then provided a brief overview of CDMRP and GWIRP funding history and award mechanisms before reviewing the Gulf War research currently funded and recommended for funding by CDMRP. For Dr. Forsythe's presentation, please refer to **Appendix A – Presentation 2**.

Dr. Forsythe explained that all of the GWIRP award mechanisms were negatively impacted financially by the sequester that took place in early October 2013 and resulted in a loss of about 7.5% in total funding. However, the CDMRP was pleased to still end up with about $20 million in total funding dollars. Dr. Forsythe discussed currently funded studies including the two GWI consortia studies led by Dr. Sullivan and Dr. Mariana Morris. She also discussed current treatment trials including acupuncture and new drug treatment therapies that were recently funded.

The GWIRP investment strategy for FY13 was then presented to the Committee members and meeting attendees. For FY13, the CDMRP will use a three-pronged approach including identification of effective treatments for GWI, improved diagnostic testing for GWI, and improved understanding of GWI pathobiology. Dr. Forsythe concluded her presentation and asked for questions.

Dr. Steele asked how large the applicant pool has been this year, and whether it has been growing from year to year. Dr. Forsythe stated that she could not give out exact numbers, but she said that the year to year application pool numbers have remained relatively stable, but the quality of the applications coming in from year to year has been increasing.

Dr. Sullivan raised the point that the consortium was extremely helpful in starting to bring people together to develop biomarker and treatment plans with collaborators that normally would not work together. Dr. Forsythe agreed that the collaborations that the consortium studies have brought about would not have happened six or more years ago when the program began.

Dr. Jesse noted that this work is very important for clinical trials, because bringing basic science findings into the clinical environment requires a unique skill set, and these programs help to bring people with these skill sets together.

Update of VA ORD Gulf War Research Portfolio

Dr. Victor Kalasinsky, VA Office of Research and Development

Dr. Victor Kalasinsky presented an overview of the VA Gulf War Research Portfolio. Please see **Appendix A – Presentation 3** for his presentation slides, and **Appendix B** for an overview of VA Gulf War Portfolio funding 2013-2014. He began with a brief overview of VA Office of Research and Development (ORD) Research. Within the ORD, there are four sub-departments: Biomedical Laboratory Research and Development (R&D), Clinical Science R&D (which includes the Cooperative Studies Program (CSP)), Health Services R&D, and Rehabilitation R&D. In terms of Gulf War Research, the requests for applications (RFAs) have been in the Biomedical Laboratory R&D and the Clinical Science R&D.

Dr. Kalasinsky then highlighted the parts of the VA Gulf War Strategic Plan for 2013-2017 and provided an overview of what has been done with respect to the plan in the past year. He stated that the VA contracted with the Institute of Medicine (IOM) to develop a Case Definition of CMI in 1990-1991 Gulf War Veterans with results still pending. Current topics for selected funding for the Gulf War research portfolio include: Gulf War Exposures and Reproductive Risk, as well as Gender Differences in Patient Symptoms. A number of Gulf War Research Projects have been recently completed. The Cooperative Studies Program (CSP) Gulf War Era Cohort and Biorepository had its kick-off meeting in August 2013, and will be enrolling participants in the near future. The Gulf War Research Portfolio Criteria for Inclusion are: Studies of CMI affecting GW veterans, conditions and/or symptoms occurring with higher prevalence in GW veterans, and long-term health effects of potentially hazardous substances. Dr. Kalasinsky concluded his presentation and asked for questions.

Rev. Graves asked for clarification on a study whose title suggested that it was being performed with Operation Enduring Freedom (OEF) and Operation Iraqi Freedom (OIF) veterans and not with Gulf War veterans. Dr. Kalasinsky replied that the study did include OEF/OIF veterans but it also included a group of Gulf War veterans (1990-1991) paired with OIF veterans.

Dr. Klimas then asked whether the multiple sclerosis (MS) studies that Dr. Kalasinsky mentioned in the VA funding portfolio included Gulf War veterans. Dr. Kalasinsky replied that in the studies that were not pre-clinical (i.e. cell-based studies), that there were Gulf War veterans included. Dr. Klimas asked why the study titles said MS and not Gulf War illness. Dr. Kalasinsky replied that MS is an illness that re-occurs in higher prevalence in Gulf War veterans.

Mr. Bunker noted that MS is specifically excluded from being able to be claimed as an illness for Gulf War veterans. Dr. Kalasinsky noted that this didn't mean that Gulf War veterans don't have MS and that there were questions and concerns whether those illnesses similar to MS are the same in Gulf War veterans as they are in non-Gulf War veterans.

Dr. Sullivan noted that these studies are often not broken down by Gulf War deployed veterans or non-deployed veterans; they are just classified as Gulf War era making comparisons of the

groups impossible. Dr. Sullivan asked whether the annual report to Congress would soon be available to the public. Dr. Kalasinsky replied that it would be posted on the website shortly.

Dr. Steele asked why there was a shift from not informing the Committee about what projects were approved for funding until they are just about to start. Dr. Kalasinsky stated that he has not released this information because it is not ready for public release and as the Committee has public session meetings, he could not release the information in this format. There was discussion on the potential of having closed sessions to discuss the recently recommended for funding projects. Dr. Timothy O'Leary made a point of clarification, that the records control schedule defines what information can be released publicly, and that this must be followed.

Chairman Binns asked whether the law enacted by Congress in 2008 requiring VA to contract with the IOM for the study on the prevalence of MS, Parkinson's disease, brain cancers, as well as central nervous system abnormalities that are difficult to precisely diagnose, in Gulf War and in recent Iraq or Afghanistan war veterans, has been funded. Dr. Kalasinsky replied that they have not entered into that contract.

Dr. Klimas asked how to start the process of allowing other investigators to use the large data sets that the VA has available. Dr. O'Leary discussed the data use agreement memorandum concerning the release of information, and the challenges and steps one must go through for this information to be able to be released. He raised the issue that veterans are a small population, and thus, a thoroughly vetted de-identifying process must be completed. Dr. Klimas stated that these data sharing agreements have already been made in some cases. Dr. O'Leary replied that they have been done within the Cooperative Studies Program (CSP), but these agreements are changing constantly, and it is important to make sure that qualified researchers will meet the confidentiality requirements.

There was then discussion on patient case labeling in the VA electronic medical record. The committee was informed in an earlier meeting that Gulf War veteran identifiers would be used in all electronic records moving forward. This apparently was still not happening. Dr. Golomb stated that she believes there is cause to distinguish Gulf War illness from other conditions, and there are multiple ways of doing so if there is a will to do it.

Ethics and Federal Advisory Committee Training

Mr. Jonathan Gurland & Ms. Jessica Tanner, VA Office of the General Counsel

Ms. Jessica Tanner provided a Federal Advisory Committee Act (FACA) overview for the Committee. An advisory committee is any committee, board, commission, council, conference, panel, task force, or other similar group which is established or utilized by the President or by an agency official; for the purpose of obtaining advice or recommendations and which has at least one member that is not a Federal employee. For Ms. Tanner's slides, please refer to **Appendix A – Presentation 5**.

Mr. Jonathan Gurland then began the ethics training. The slides for this presentation can be found in **Appendix A – Presentation 4**. This was meant to provide the members of the RAC with ethics training for Special Government Employees (SGE). An SGE is considered an advisory committee member that does not serve more than 130 days during a given year's period of time; this can be with or without compensation. Mr. Gurland discussed all the current rules and regulations pertaining to SGEs.

Committee Discussion: 2013 Committee Report

Mr. James Binns, Committee Chair
Dr. Roberta White, Scientific Director

Prior to beginning Committee Discussion, Rev. Graves and Mr. Bunker both made statements. Rev. Graves began his statement, and noted that this meeting may have been his last. Rev. Graves stated that his unit was one of the first to deploy to Saudi Arabia. He reported that prior to Operation Desert Storm, he was a high functioning individual. The war changed this for Mr. Graves. He didn't realize that the chemical alarms were significant until his unit members became sick, and his own ability to function began to decline.

Years later, he was asked to become a Committee member. Over the course of his twelve years on the Committee, he has experienced the frustrations of presenting evidence to the VA and not seeing any action in response. The Committee has been looking at what a case definition should be for GWI, and over the years he has put together categories and subcategories of characteristics. He provided examples of each category and how soldiers experienced them in theater. He explained that environmental stressors and exposures were important to long-term health of GW veterans.

Rev. Graves said that the VA and Department of Defense (DOD) told the veterans that they had been exposed to sarin, but to insignificant amounts. He then stated that the Committee has learned over the course of its life that even small exposures can cause significant effects on the human body. He stated that he had first-hand experience of the chemical weapon exposures and that it was real and should be taken seriously. He stated that he has never woken up one day since the war, and thought he's all better. He has just learned to live with it. That is why this Committee is so relevant after this long. Rev. Graves continued that the VA and Congress need to trust the Committee to do its job, and they need to act on the Committee's recommendations.

Mr. Bunker then made a statement in support of Rev. Graves's comments. He said that the GW theater was found to have contained chemical agents including sarin and cyclosarin, both having been released while troops were there. He said that the DOD has stated that there were no cases of acute organophosphate poisonings reported, which he said is not true. Mr. Bunker reported being given two shots of atropine prior to being put on a helicopter; after he experienced

symptoms including dizziness, vomiting, headaches, and loss of muscle control in the GW theater. He said that he was never told what the type of nerve agent that he was exposed to, but that he had to be taken out in a helicopter. He reported that he has gotten better in recent years and no longer requires crutches to walk but that his cognitive symptoms have continued. Mr. Bunker suggested that others should not criticize VA because those who criticize are not looking for solutions either and that everyone should work together.

Following Rev. Graves and Mr. Bunker's comments, Chairman Binns prefaced the Committee discussion by thanking those who participated in the draft report. Chairman Binns reminded the Committee that recommendations should be discussed in a public meeting, and would be discussed in this session. He anticipated that changes and additional recommendations would be made before the final copy of the report was released, and asked that individuals make recommendations as specific as possible.

Chairman Binns noted that some Committee members had questioned the last section of the draft report that reviewed federal research programs, in light of the change made to the Committee charter by VA in May 2013 eliminating the Committee's authority to review the effectiveness of government research programs. Mr. Binns asked Dr. Kalasinsky if that charter change had been rescinded, and Dr. Kalasinsky replied that it had not. Chairman Binns stated that it accordingly was necessary to remove the section, and not to consider it in the report.

Dr. Roberta White began deliberation and discussion on the *Gulf War Illness and the Health of Gulf War Veterans: Research Update and Recommendations, 2009-2013* draft report. The purpose of the report was to review the science in this area for the last five years, since the 2008 report. She covered what would be the draft review process moving forward. During the Committee meeting, the report would be reviewed by sections. There would be a focus on the conclusions and recommendations for each section, and edits/revisions would be discussed. She stated that on January 22, 2014, written edits and suggested revisions would be due from RAC members. The next draft would be circulated after these edits were received. The Committee hoped to have the final report ready for release in April 2014. For discussion slides, please refer to **Appendix A – Presentation 6** and **Appendix A – Presentation 7**.

The report draft consisted of four content sections. The first section covers Epidemiologic Research; the second section covers Etiological Investigations; the third section covers Pathobiology of Gulf War Illness; and the fourth section covers Gulf War Illness Treatment Research.

The draft report followed with a discussion of the Federal research programs that addressed the health of 1990-1991 GW veterans, but that section was now removed. The draft report then discussed Research Priorities and Recommendations. The draft report included four appendices, including the Draft Strategic Plan for Gulf War Illness Research, a complete list of Committee

Members, a Committee Charter, and an Appendix that discussed the Effects of Pesticide Exposure in Non-Gulf War Cohorts.

Discussion and deliberation then commenced. Dr. White, Dr. Jim O'Callaghan, and Dr. Lea Steele each presented sections of the report to be reviewed and gave the Committee members and opportunity to ask questions or suggest edits to each section.

Dr. O'Callaghan began by reviewing Section 2, Etiology. He explained that the animal models of GWI that have been used and published over the last five years reflect effects in different body systems but most studies have been nervous-system related. New research approaches have recently been implemented including proteomic and genomic profiling and several new mechanisms have been implicated in GWI animal models. There have been indications that neuroimmune and neuroinflammatory mechanisms are involved in GWI in addition to changes in key aspects of mitochondrial function. The section was divided into exposures and studies published since the 2008 report. These studies continue to support exposure to pesticides and PB as etiologically important in development of GWI and the behavioral and cognitive dysfunction seen in GW veterans.

The summary of literature review of human studies followed. Those first reviewed included sections on pesticides and PB, nerve gas agents, and oil well fires. Vaccines, depleted uranium, and complex exposures followed.

The next section reviewed was research findings in animal models. Dr. Klimas suggested that a disclaimer or note be added for the report reader to be able to understand that the animal studies are a means to get to promising human studies faster.

Research recommendations in animal models were then reviewed, during which Dr. Golomb stated that she believes emphasizing a broader range of objective markers rather than getting too specific is important.

There was discussion on specificity regarding translation between animal models and human models. Dr. O'Callaghan discussed that the knowledge of what constitutes Gulf War illness in living ill veterans is trying to be modeled in the animal studies. What is key, then, is an explanation of how end points relate to exposures and persistence of the effects in the model that relates to Gulf War illness. There was also discussion about combining the human and animal models with regard to outcomes and exposures.

Research findings in human models were then reviewed and research recommendations were reviewed. Dr. Steele posed a question regarding the association between vaccine exposure and Gulf War illness, noting that no association given current research to date had been found. Dr. Golomb thought it would be important to include this. Chairman Binns asked for clarification on whether this sentence was consistent with the 2008 report findings, or whether it was an update.

Wording was discussed. The Committee agreed to include specific wording on the need for more information in the recommendations section with regard to vaccines.

Dr. Klimas asked a question about the second point in the recommendations section, on the wording regarding biomarkers. Dr. White agreed to make this point more specific so as to avoid questions in meaning. Mr. Graves had a question to the third point, regarding including more of the different environmental exposures. This was agreed upon; Dr. White stated that she would add more exposures to this section.

Chairman Binns asked whether it was important to prioritize the recommendations and discussion followed. This question was held until the following day for discussion, as the epidemiology section needed to be started.

Following the full review and discussion of Section 2, Dr. Lea Steele began the review of the Epidemiology research and recommendations section of the report draft. She began with an epidemiologic research overview and update. There was an extensive body of epidemiologic studies prior to the 2008 report, from which the committee drew conclusions, and recommended research to address high priority issues. Since 2008, there has been limited epidemiologic research. In the draft report findings, an update was provided on what has been learned from those post-2008 epidemiologic studies, and there was a recommendation for both priority research and methodological improvements that are still needed.

Dr. Steele then covered the major findings and issues included in the epidemiologic research component of the 2008 RAC report. There have been multiple large studies of diverse GW veteran populations. With regards to mortality, no overall increase in disease-related mortality has been found. Little research or systematic data have been used to determine if GW veterans have excess rates of most medical conditions of concern. Studies indicate ALS rates are significantly higher than in other veterans. There is a possible increase in asthma for the group with the greatest amount of oil fire exposure. Studies have shown an increase in CFS and FM. GW surveys indicated a significant increase in veteran-reported medical diagnoses: migraines, gastrointestinal conditions, respiratory conditions, skin conditions. There were limited differences between GW deployed and nondeployed veterans.

With regards to the health of GW veteran family members, the data are inadequate on birth defects in children of Gulf War veterans. There are serious methodological issues in GW epidemiologic research: including a lack of research guidelines and standards, inconsistent health and outcomes measures, failure to assess outcomes in subgroups of interest and little control for confounding.

Recommendations for epidemiologic research included: a regular longitudinal assessment of veterans to assess GWI over time. There should be regular monitoring. There should be further evaluation of birth defect findings, and data available on family health should be published. There were also recommendations for improved methods in GW epidemiologic research.

Dr. Steele then discussed an overview of epidemiologic research to the current date. There has been considerably less published GW epidemiologic research since 2008. The VA GW Strategic Planning process included plans for improved surveillance of health outcomes, and for establishing expert-consensus case definitions for GWI. Little additional information on the long-term prognosis of GWI has become available since 2008. She suggested that prior data suggest that there is little to no improvement in the health of ill GW veterans over time and the effect that aging will have on this vulnerable population remains unclear. Despite the extensive number of studies conducted with Gulf War veterans in the 23 years since Desert Storm, medical surveillance in this population remains inadequate.

With regard to medical conditions in GW veterans, little research has been conducted to determine rates at which veterans have been affected by medical conditions of possible concern. Disorders of concern reviewed in this report included neurological disorders and cancer. In general, rates of most medical conditions remain unknown and understudied.

It may be necessary to consider Gulf War veterans who do and do not meet criteria for these disorders separately in research studies of GW veterans, including treatment research. Studies on psychiatric morbidity in deployed Gulf War veterans since 2008 continue to show that combat and other wartime stressors are associated with PTSD, anxiety, depression and alcohol abuse but do not predict or explain Gulf War illness.

Dr. Steele stressed that the complete lack of current information on overall and disease-specific mortality among U.S. Gulf War veterans remains an important issue. No comprehensive information has been published on the mortality experience of U.S. Gulf War era veterans after the year 2000. Despite specific recommendations, over many years, from both the current Committee and Institute of Medicine panels, federal research efforts to monitor the mortality experience of 1990-1991 Gulf War veterans remains inadequate.

Public Comment

Mr. Ronald Brown, president of the National Gulf War Resource Center, submitted a written comment which is listed in **Appendix C**. He then summarized his written comments. He explained that the Forgotten Warriors II Program was created to help the VA better serve the needs of sick Desert Storm veterans. This program asks sick Desert Storm and Desert Shield veterans what they believe is the most important thing for the VA to do to help them. He stated that better primary care physician education was crucial. Veterans told him of physicians discarding research and information that veterans had provided to them, and a complete lack of knowledge about the VA War-Related Injury and Illness Study Centers (WRIISCs) by VA physicians. He stated that research is only helpful when it can be applied by medical professionals treating the veterans.

Mr. Brown gave an example from his own treatment for his severe fibromyalgia. He asked his physician for a referral to rheumatology for better treatment, and was denied the referral because his PCP stated that his condition was inflammatory. He now travels to Washington, D.C. at his own expense for this treatment. He finds it unacceptable that he has to seek treatment outside of the VA for a service-related illness.

Mr. Brown also stated that there was a problem with the social guide that is given to VA employees. This publication lists every medal from World War II, Korea, Vietnam, and then jumps to OEF/OIF veterans. The Gulf War medals are missing entirely. This is why the project is called the Forgotten Warrior Project II. He stated that men and women service members stepped forward without hesitation when they were called upon by the United States during the Gulf War. Yet, 23 years later these individuals still fight for adequate care, and are not given it. He stated that this program is about building a better relationship with the VA, not criticizing it.

Maj Denise Nichols then made a public comment. She stated the importance of updated data on diagnosed illnesses that are occurring in GW veterans. She stated that hypercoagulation was important in GW illness research. Maj Nichols stated that Dr. Ronald Bach, had developed a commercially available test for hypercoagulation in GWI and that this research has now been published. His research had shown that there are GW veterans with cardiac issues, pulmonary embolisms and strokes that could be related to hypercoagulation. She stated that she was disappointed that the VA was not utilizing Dr. Bach's hypercoagulation test in the clinics. She stated that when veterans subject themselves to research, they should be provided with a report on that research. She expressed her disappointment that the veterans are not being better taken care of. She also asked that VA should not say that there will be no more presumptives for ill GW veterans.

Mr. Paul Sullivan prepared a written statement for the Committee, which can be found in **Appendix C**. The following is a brief summary of his statement. Mr. Sullivan is a GW veteran, and is on the Board of Directors for Veterans for Common Sense. He thanked past and current members of the Committee, and welcomed all new members. He explained that he worked on the legislation that created the Committee; he wrote the first charter and had attended most meetings. He stated that the Committee should cover the issue of the effectiveness of federal research for GW illness research, and he was very disappointed that the VA had not fixed the recent changes to the Committee charter and that the VA would not accept the findings of the Research Advisory Committee regarding the effectiveness of federal research. He believed that displayed VA's intent to block research on GW illness. He explained by altering the charter, VA had blocked the ability of the Committee to do as it was originally meant to function.

He stated that veterans want to know why they are ill, how they will get better, and who will pay for their care. He believed that the VA was still blocking research, treatments, and disability

benefits and that VA was not being transparent which will be hamper any efforts to prevent future illnesses of similar toxic exposures. Mr. Sullivan stated that Congress had acted repeatedly on this issue because the VA had refused to help GW veterans. He stated that veterans were still being denied benefits for the disability claims and that the previous month, Ms. Allison Hickey, the undersecretary of benefits, had made this situation worse. She said the primary goal of her agency was to eliminate backlogged claims, and that the only way to do this would be if there were no new presumptives. He stated that was unconscionable to have a political decision that stops the science and health care for veterans. Mr. Sullivan concluded with closing comments. At the last meeting he attended the VA claimed to have changed the Committee because the Committee had acted outside of the bounds of their charter. Yet, when pressed for examples, VA provided none. Mr. Sullivan stated that GW veterans have tried to meet in good faith with the VA, and VA leaders have not met with them except once. He explained that the VA had not responded to his letters, to veteran's letters or to any of the Committee recommendations in the past ten years.

The public comment was then opened for those calling in to the meeting by telephone.

Mr. Peter Green stated that he is an ill GW veteran, who has recently served as a CDMRP consumer reviewer. He reiterated Mr. Brown's comments about communicating research efforts to primary care physicians. He felt that there was a lot of money being wasted on treating symptoms and that this was costing GW veterans their lives and it needs to be fixed. He made a second point, questioning the VA on a recent issue that came to light. Dr. Steven Coughlin had previously alleged research violations at the VA Office of Research, and the Office of Research oversight claimed that they would conduct an investigation. Mr. Green had learned from two reputable sources that this investigation had been completed, but it was not released to the public. He stated that multiple emails and Freedom of Information Act (FOIA) requests had been ignored. He asked if VA could update the status on the report.

Dr. Jesse answered Mr. Green by stating that the report had in fact been completed and was going through the legal and standard processes before it could be released. He stated that the report would be released as soon as this process had been completed and there was no intent to hold-up the release of the report.

Mr. Douglas Bartholomous then spoke about his difficulties with his local VA to get compensation for his PTSD and Gulf War Illness claims. He thanked the Committee for their efforts in GWI research. He stated that there were many times that he felt hopeless, but that he needed to stick it out to set an example for his ill brothers and sisters from the GW. He urged the VA to help GW veterans before it was too late.

The next caller, Mr. Glenn Stuart, echoed Mr. Brown's sentiments agreeing that his primary care physicians did not know what they need to be doing with regard to treating GW veterans, and that the VA needed to change this. He explained that his primary care physician would not refer him to the WRIISC because he thought it was the same as the GW registry examinations. He also echoed sentiments on presumptives for GWI stating that all claims that he has submitted have been denied.

Mr. Curt then spoke for public comment. He thanked the Committee members for attending the meeting. He also submitted an email for the public record that can be found in Appendix **C**. He mirrored the conclusions that Mr. Paul Sullivan, and echoed that the problem was at the executive level of the VA. He stated that the Committee has repeatedly tried to make recommendations, and the VA has ignored them. He believed that this should become a legislative issue to return the original powers back to the Committee.

Mr. David Lachelle made the next public comment. He stated that he had heard many things in the last three meetings that he had not heard before with regard to GW illness. He complimented Dr. Golomb, because he used her paper with his primary care physician and it changed his physician's opinion of GWI. He also stated that Dr. Klimas' comments on immune disease struck home for him. He has rheumatoid arthritis, and despite trying different treatments, his condition was only worsening. He thanked the Committee for all of their hard work despite the adversity they face.

Mr. Kip Schultz spoke for public comment. He worked with explosive detection dogs while deployed in Kuwait. He doesn't go to the VA, and presents will similar symptoms that the other veterans had discussed. He had looked through the working dog study of animals taken to Lackland Air Force base for study. He asked if there were plans to study these 118 animals further with the new information learned over the past ten years.

Dr. Steele responded that the Committee was not aware of any proposals or plans in the pipeline to study those dogs. She asked Mr. Schultz if he knew either the breed of dog, or whether they would still be alive at this point.

Mr. Schultz responded that he believed most of the dogs had been euthanized, but he would assume that they have medical records of tests done with the animals. He stated that there were good researchers there who could go back to the records and look at which dogs were in the GW while the exposures were occurring, and see how they were affected. He stated that the results would obviously be diluted because all of these dogs came from different places however.

Dr. Victoria Davey, director of VA Office of Public Health (OPH) then answered Mr. Schultz. OPH currently has an ongoing study of military working dogs whose records are located in the

same timeframe. She explained that the study was examining necropsies of the dogs, and the removal of endpoints (including respiratory or pulmonary effects, and other organ effects). The study was still underway, so the data release date was unknown at this point.

Mr. Schultz asked Dr. Davey if this study included dogs that served in the GW. Dr. Davey replied that they were from as long as the records were available. She stated that this was the canary in the coal mine study, and results will be reported to the Committee as soon as data are available.

Mr. Mike Jarret was the final speaker for Monday's public comment. He asked the VA individuals present at the meeting for their help. He addressed several of the issues that Mr. Brown had brought up. He spoke about the GW registry exam. He called the environmental people at the VA and they knew nothing about it. That was in West Virginia. Southern Virginia facilities didn't know about it either. He stated that there was a backlog of over two years at both facilities mentioned.

He mentioned that there was a high turnover rate at VA. Mr. Jarret went to New Jersey because they had the mitochondrial research institute. He brought pamphlets back, because they are having trouble getting the word out for participants. VAMCs are not communicating with each other. He went into his VA the day before to get blood work done, and the New Jersey center information was not posted anywhere. This research can help GW veterans immensely. There are a number of small steps that the VA could take to fix this, because there are a lot of people that are willing and wanting to get involved.

Dr. Jesse thanked all of the speakers, and reiterated that he heard all of the issues that the veterans were communicating, and that he hoped that during discussion the following day that he could raise all of these points, and address the comments.

Chairman Binns closed the session at 5:30PM. He stated that the meeting would reconvene on Wednesday morning, at 8:30AM.

DAY 2

The January 8th, 2014 meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses (hereinafter referred to as the Committee) was held in the Sonny Montgomery Room (Room 230) at the U.S. Department of Veterans Affairs Central Office, 810 Vermont Avenue, NW Washington DC.

Introductory Remarks

Mr. James Binns, Committee Chair

Chairman Binns welcomed all participants to the second session of the January 2014 RAC Meeting. It was announced that upon Dr. Broderick's arrival, he would present his work to the committee and audience members. Following Dr. Broderick's presentation, the committee would continue their draft report discussion from where it left off at the prior day's meeting.

Identifying therapeutic strategies in Gulf War Illness with systems biology

Dr. Gordon Broderick, Nova Southeastern University

Dr. Sullivan introduced Dr. Gordon Broderick, Professor of Psychology at the Institute for Neuro-immune Medicine, Nova Southeastern University.

Dr. Broderick thanked the Committee for the invitation to speak at the Committee meeting. For Dr. Broderick's slides, please refer to **Appendix A – Presentation 8**. Dr. Broderick began by noting that Gulf War Illness spans across multiple regulatory systems, each of them working in a highly integrated and highly complex regulatory network. The regulatory system in the body can successfully run more than one regulatory program. The objective of these programs is to resist change and bring the body back to a stable resting state. In response to a challenge, the regulatory system will react in order to bring the body back to normal function. If something pushes the system too hard, it can be moved beyond the normal regulatory "regime" into a new "regime", which can be compared to a stable adaption response, which gives rise to a new set of rules and behaviors. At this point in time the regulatory system is now working by a new set of rules, which give rise to a new set of response dynamics.

Local response dynamics were generated by Dr. Broderick's team in order to investigate this change, by introducing a maximal exercise challenge. Co-expression patterns of these markers showed that in GWI compared to healthy controls, there was an emergence of patterns that were extremely different from the healthy controls. The immune markers and endocrine marker patterns were markedly different. Interluken-1 (IL-1) was identified as something to examine that might be a trigger.

Dr. Broderick's team has been monitoring markers at the intercellular levels, doing gene expression, micro-RNA, and looking at changes in cell population in cell-cell signaling. The responses are quite different continuously between GWI and control participants in terms of magnitude and dynamics of immune response to exercise. This information can be used to map out a circuit that captures the flow of immune information between immune cell populations. His latest results suggested that NF-kB activation was a primary central inflammatory driver in GWI.

In parallel to this work, they looked at what in terms of illness processes that GWI might share with other illnesses. He thought that this might help in identifying current treatments that might

be borrowed to help provide relief to those living with GWI. He stated that GWI orbits one of the stable operating regimes in systems biology. The major variant was persistent pro-inflammatory signaling. He stated that finding the correct path in treatment methods is the key, and is the concept being pursued to develop the correct treatment plan for GWI. He suggested that more than one angle of attack would be necessary to resolve GWI, and that so far no viable single-point intervention will allow for an escape from the regulatory pull. Dr. Broderick concluded his presentation, and asked for questions.

Mr. Bunker asked for clarification on the case definition used for GWI patients and for controls in Dr. Broderick's studies. Dr. Broderick asked Dr. Klimas to respond to this question. The controls were GW-era healthy veterans, who were not necessarily deployed, were very tightly matched in age, smoking and alcohol consumption. For the GWI case definition, a combination of the Fukuda criteria and the early Haley criteria was used. She said that the study participants were GWI patients.

Mr. Bunker asked whether this study would be moving beyond the pilot stage. Dr. Klimas said absolutely they would like to continue this project forward, and that they would be trying to get to human trials by the fourth year if at all possible. This has been critical research in working to bring the animal and human models together and to figure out what is stable, what is not stable, and how to re-stabilize these systems to bring the model back to the healthy state.

Dr. Sullivan asked whether there were any other examples of this type of modeling used to identify new treatments for difficult illnesses. Dr. Broderick responded that he had not heard of other research being done like this before where the model was brought all the way into clinical practice. Dr. Klimas noted the importance in future research of writing grants that would incorporate different disciplines. She stated that there have been problems with being able to get funding that is so interdisciplinary. She posed the question of whether there is any way to expedite and streamline this grant acceptance process. Dr. Jesse picked up that question, noting that it is difficult to be able to see a fully ready grant. Many people write very good grants that will not produce the most relevant work, and those that have brilliant ideas, but don't write the grant well. This is often the difficulty in trying to find the balance in choosing which are the best grants to fund.

Committee Discussion: 2013 Committee Report

Mr. James Binns, Chairman
Dr. Roberta White, Scientific Director

Dr. White began with an overview of the draft report review discussion, explaining that the Committee would review the methodological issues, research findings and recommendations sections, and then discuss any suggested edits. She then turned the discussion over to Dr. Steele to begin the remainder of her section.

Dr. Steele continued her discussion on the epidemiology section of the draft report. She stated that edits would be content and wording specific.

The collection of data on GWI has been hampered by a number of methodological issues relating to case definitions, concurrent disorders and conditions in ill veterans, multiple exposures, subject recruitment, subject follow up and survey tools. Whether these groupings are based on exposure, unit membership, symptom profiles, deployment location or a combination of factors, comparisons of subgroups with healthy controls will be more informative than assessing deployed veterans as a single group. This has been a finding in previous reports as well, and has been raised by the Committee for many years.

Case definitions currently include the Haley syndrome criteria, the Fukuda et al (CMI) criteria, the Kansas GWI definition and other adaptations of these approaches to defining GWI. Many research papers and proposals do not clearly define the criteria used for identifying veterans with GWI. In the absence of a consensus case definition 22 years after the appearance of this condition, it is difficult to compare findings in research approaches to Gulf War illness.

Relatively little data are available that provide a clear understanding of the impact of Gulf War service on the current health of Gulf War veterans. Some of these issues are addressed in the VA longitudinal survey currently underway, but the survey instrument does not allow identification of veterans with GWI and other outcomes of interest. Information about GWI prevalence and prognosis as well as other medical disorders is the key to healthcare planning for this population.

Dr. Steele then began to discuss epidemiologic research recommendations. She asked that any questions or discussion points be raised as she covered each recommendation. The Committee recommended that the VA implement the steps outlined in the draft strategic plan for developing an evidence-based, expert consensus-driven case definition for GWI.

The VA should cancel the current IOM assignment to develop a Gulf War illness case definition, since it will not be developed using an evidence–based process that includes analytic assessment of data available to evaluate and optimize the definition. The VA should adopt the name Gulf War illness for the symptomatic condition associated with military service in the 1990-1991 Gulf War.

With regards to surveillance, ongoing monitoring and surveillance of the Gulf War veteran population is critical as this group of veterans age. Such surveillance must include the following: ongoing assessment of Gulf War illness and its impact on the health and lives of GW veterans, a systematic assessment of overall and disease-specific mortality in GW veterans in specific subgroups of interest, the use of VA's longitudinal survey to assess rates of physician-diagnosed medical conditions in Gulf War and era veterans is important, the use of VA's longitudinal survey to assess rates of health problems and birth defects in children of Gulf War era veterans is also important, and there is needed evaluation of health outcomes in Gulf War veterans in subgroups of potential importance.

Dr. Steele then covered the recommendation for improved methodology in GW epidemiologic research. It is important that VA work with CDMRP to establish guidelines for improved methodology in Gulf War research that can be included in requests for proposals and subject to research application reviews. Such guidelines should include the following: systematic methods for assessing symptoms and other health outcomes in GW veterans, the evaluation of health outcomes in GW veteran subgroups of importance, there should be a consideration of subpopulations with multiple health outcomes, use of analytic methods that adequately control for confounding effects of additional exposures and etiologic factors. Dr. Steele stated the need for a systematic symptom inventory. Surveillance for both GWI and for other conditions is very important.

There was a question from Ms. Denise Nichols regarding the IOM report. It was the audience member's understanding that the report had been completed and already submitted to the VA. She stated that it might be important to include in the report that this IOM report may be released soon. Another audience member, Gulf War veteran Julie Mock, requested the inclusion of children's research to include neurological anomalies, such as mitochondrial illnesses. Dr. Steele stated that she would like to know more about the research and any new findings, and if in accordance with the Committee, would be willing to add that surveillance of children with associated problems to the report. This was agreed upon by the Committee before going to a short break.

After the break, Dr. White began by covering the research section 3, pathobiology. The summary section consisted of four sections including imaging and EEG, cognition, neuroendocrine function, and immunological function. Dr. White then covered the conclusions and recommendations section of the pathobiology section. She covered research findings for imaging and EEG parameters, studies of veterans with GWI defined in various ways. She covered cognitive abilities. Studies on cognitive function in Gulf War veterans continue to support the conclusion from the 2008 report that cognitive dysfunction is a central issue for Gulf War veterans with Gulf War illness and with specific exposures in theater.

With regard to neuroendocrine function, studies support altered HPA-axis functioning in GW veterans that is not consistent with the typical pattern seen in post-traumatic stress disorder (PTSD). Recent studies also showed immune dysfunction. Research in this area appears to be narrowing in on changes occurring to the expression of certain cell lines. She then discussed research findings in the report, in terms of each of the four sections previously covered. The recommendations followed, including the development of clear case definitions, addressing theater exposures, considering variables in mechanistic studies, and utilizing animal models for investigation of mechanistic hypotheses.

Dr. Klimas recommended that more extensive research should be done regarding gender variations. Dr. Golomb agreed that there needed to be more research on gender differences. There was a question whether gender should be made into a separate recommendation, in

addition to a systems biology recommendation. Dr. Golomb stated that she believed that systems biology was only as good as the data that went into it. She believed that it may still be too early for this. Dr. Broderick agreed on this point. He believed that the emphasis should be on the data and more time course studies that focus on the regulatory dynamics. Dr. White asked the Committee members to send any specific recommendations to the RAC office by January 22nd.

Discussion then continued regarding the biorepository data and adding a recommendation specifically related to the implications for using them. Dr. Crawford agreed that this was very important, especially regarding human studies. Dr. White thought it was important to use tissue samples for biomarker studies of Gulf War illness. She asked Dr. Crawford to devise a recommendation for this and Dr. Crawford agreed. Dr. Klimas also agreed to write a recommendation regarding gene expression studies. Dr. White highlighted the next steps of editing the draft report and putting out another draft for the next meeting. Dr. White stated that the final report would be ready by the April meeting.

Ms. Denise Nichols asked for the Committee to compare data on women and men on reproductive issues. Early miscarriages, hysterectomy, and other difficulties have been reported. The audience member suggested that the report should mention that these problems have been experienced by GW veterans, and the Committee should consider at least identifying which tissues should be saved for the GWI biorepository or data should be collected before it is too late.

Dr. White then discussed research section four, treatment research. A treatment research summary was provided including that since the 2008 report, a number of treatment studies have been completed. These studies included: an amino acid supplement containing L-carnosine, continuous positive airway pressure (CPAP), and co-enzyme Q10 (CoQ10). Ongoing treatment studies included: probiotics, light emitting diodes (LED), repetitive transcranial magnetic stimulation (rTMS), resistance exercise training, acupuncture (with and without additional therapies), acupressure, nasal irrigation, a detoxification protocol, mindfulness-base stress reduction (MBSR), mind-body bridging (MBB), and problem solving cognitive therapy.

Since the 2008 report, a number of animal treatment models have been studied. Dr. O'Callaghan is currently studying minocycline as a potential treatment to reduce neuroinflammation in an animal model of Gulf War illness. Dr. Abou-Donia from Duke University Medical Center is testing flupirtine in animals exposed to pesticides. Another study by Dr. Ashok Shetty is examining the relationship between anti-depressants, antioxidants, and exercise.

Discussion began on treatment conclusions and recommendations in research findings. Dr. White covered research findings, and then recommendations. The recommendations included the approaches that should be taken in treatment research, including clear case definitions, objective outcomes for functional improvement, and improvement in underlying expressions of pathology. Additionally, treatment approaches based on known mechanistic pathways of GWI, biomarker based treatments and gene-based therapy approaches were also included.

Committee discussion followed. Dr. Steele stressed that it is really important to have some mechanism where researchers evaluate good ideas and get some pilot data on those ideas to turn into larger trials later. CDMRP has methods for clinical trial planning. Preliminary studies are important. A recommendation was discussed to add smaller scale studies that would help to identify candidate therapies to turn into larger scale treatment trials. The VA does not have methods for funding these pilot studies and adding them couldn't help to multiply the viable studies and ongoing treatment research. Dr. Golomb and Dr. Sullivan agreed. Dr. Golomb then suggested a wording change regarding alternative therapies.

Dr. Kalasinsky spoke to the small clinical trial issue regarding power and safety. He stated that if a pilot is truly a pilot project, there is a concern for the safety of patients. Dr. Steele stated that if there is a trial for which there are no preliminary data the study should be kept small. Dr. Timothy O'Leary, VA Acting Chief of Research, discussed a mechanism that is available for smaller scale trials. He stated that he agreed on the need for funding for small scale pilot studies, and that he would better publicize this award funding that is available.

Dr. Klimas said that that there were enormous restrictions on repurposed drugs in VA research, or this was at least how it was interpreted by review committees and this created a big block for researchers trying to get these small scale pilot clinical trials funded. Dr. Golomb highlighted the lack of baseline information about new drug treatment trials as well. Dr. Klimas stated that it was incredibly confusing to figure out what was available for investigators to fund smaller treatment trials and posed a real challenge for VA investigators to figure this out.

Dr. Steele stated that there was a systematic survey of treatments tried and lifestyles practiced which has been done but never published. Dr. Klimas would like to find a way to promote this information and fill in the gaps for what is currently unknown. Figuring out from individuals self-report what helps and what has not, would be very helpful. Dr. Agarwal replied that there was currently a survey underway called *Veterans Like Me*. Dr. Jesse discussed that he has not yet heard about the progress on this survey, but does not want to duplicate this work, and would like to wait and hear about what will come out of this before discussing it further. Dr. Steele replied that this has already been done and that 15,000 GW veterans had been questioned extensively, and that these survey replies had not yet been released.

Dr. Sullivan made a recommendation regarding the need for clear case definitions to be used in treatment studies. She also suggested that treatment studies should consider obtaining data on other case definitions within their cohort as well so that the study results can be compared with to one another. Otherwise the results of the studies would be akin to comparing apples to oranges. Dr. White said that the need for a clear case definition is important because often times GWI case definitions are defined based on the investigator's own definition and not a clearly defined definition. Chairman Binns contributed that it was important to say something beyond clear case definitions. Dr. Steele agreed on this point.

Dr. O'Leary posed the question of whether the Committee's direction would be facilitated by a standardized set of elements with clear data definitions and a minimal data set so that data sets from different trials can be combined. This is otherwise still difficult to do with a verbal definition. Dr. Steele replied affirmatively and stated that this was the purpose of the case definition recommendation. She stated that there was absolutely a need for the definition and criteria to be set so that researchers will always compare apples to apples.

Dr. Sullivan asked a question about treatment therapies in the draft report regarding gene based approaches. Dr. White confirmed that they were not talking about gene therapy but biomarkers from genetic studies. Chairman Binns suggested a language consistency recommendation to resolve any ambiguity. He also stated that there was a need to make sure that the recommendations wording remain consistent throughout the report.

Mr. Bunker made the point that repurposing drugs are increasingly important, and that the VA should allow for that, because timing is so short for GW veterans. Dr. Sullivan agreed. Dr. Klimas pointed out that the VA does not fund validation studies and this was absolutely necessary in looking at biomarkers and treatment plans. She stated that this recommendation was a very important one for that reason.

Mr. Ronald Brown commented that during his treatment for knee replacement surgery he had been given human growth hormone and he was doing significantly better after this treatment. He gained muscle mass, and recovery time was quick. He wondered whether this hormone had ever been tested in GW veterans. Dr. Klimas replied that she did not believe this has ever been tested on GW veterans, but had seen it used to treat chronic fatigue syndrome. She thought it was a great question that should be raised in treating GW veterans.

Dr. Sullivan asked whether recommending a certain number of treatments trials should be added to the report recommendations. Dr. White thought this would be very challenging to do. Dr. Steele suggested that she would like to see a goal for an increased number of trials done, but maybe a recommendation that mechanisms for more treatment development should be added instead of a number of trials per se.

Dr. O'Leary agreed that mechanisms like those suggested should be developed and that ORD should restructure some things to make sure that this is included. He agreed that the development pipeline would be extremely useful, and that the Committee should absolutely be apprised of these developments.

Chairman Binns believed that a recommendation should say that something along the lines of this entity should be done, but would not state explicitly those individuals who should do it.

Dr. White commented on some of the 'big picture' items, that have been listed on the slides, and that still needed to be discussed. Dr. White stated that she would like for a point to be made about validation studies, which would be worked on some more for the next report draft. She said that the Committee would generate an executive summary based on the discussions of this meeting. Chairman Binns stated that the purpose of the executive summary would be a high level inclusion of all findings, for someone who will be looking for information, but does not have time to read the full report.

Dr. White asked for discussion on prioritization. Whether the group should list recommendations in order of importance, and if so, the Committee will need to develop a mechanism for ordering, allowing members to weigh in. This method was agreed upon. Dr. White asked for the Committee to look through all tables and note any edits or inconsistencies and send them to her to add to the report edits. Dr. White then concluded the discussion.

Public Comment

Before public comment began, the VANTS line network went down because of a system error. Veterans who intended to speak over the phone were asked to email any comments to the Committee email for inclusion in the written comments section of the meeting minutes.

Mr. Ronald Brown submitted a written public comment, which he read from at the meeting. The public comment can be found in **Appendix C**. The following is a brief summary of his comments. Mr. Brown thanked the Committee and audience members for their attention. He stated that the Gulf War Review was a newsletter sent to GW veterans providing information on GW-related issues. This letter was stopped years ago, and veterans have been left confused about the VA GW programs. He stated that this newsletter was a great thing. It was designed to keep veterans informed, and was stopped without any warning or reasoning. He suggested that if it cost too much to print, why not put it up on the website? The NGWRC would like to see the Gulf War review restarted to help keep GW veterans informed on current research. It should contain current research information, and research reports and results. There should never be a lack of veteran participation, and without the Gulf War review there was. The Minneapolis VA has contacted the NGWRC to advertise research studies. He stated that veterans should be informed every three to six months about current research.

Mr. Brown stated that it does not make sense to spend money on research when there is so much more opportunities to recruit larger study groups. Researchers have such low participation because the study information is not disseminated. The NGWRC feels that the VA could do

much more, and the review letter is one way to start doing that. He thanked the VA and the Committee for their help.

Chairman Binns commented on Mr. Brown's insightful point regarding keeping veterans informed on current research that they can be involved in. There were legal and ethical issues with posting these materials on behalf of the VA, but Chairman Binns thought that making this resource privately available would be very helpful.

Dr. O'Leary made comments regarding this suggestion. He stated that there are publicly available sites regarding VA related studies that are recruiting or are in progress, but they hit a block regarding publishing any information regarding non-VA studies that are being conducted.

Mr. Keith Nordick spoke for public comment. He thanked everyone on the Committee. Mr. Nordick is an ill GW veteran. He hoped that his voice could help echo the feelings of his ill veteran brothers and sisters. He stated that GW veterans advocate for themselves daily, in hopes that physicians at the VA will realize their condition is real. Physicians he has presented to have told him he was too old to have served, and that beyond the GW registry examination that there wasn't much else that could be offered by the VA.

He said that research shows that GW veterans have an illness and that they are sick. They hope that there will be a better understanding of GWI, as they are in the last hours of the fight. Strong and dynamic leadership in the VA will be the only thing that will make this happen. The veterans demand action from the VA to improve health, with emphasis on research and treatments recommended by the Committee. He suggested that the veterans start a petition to the Secretary of the VA to keep Chairman Binns on the Committee in his current capacity. He believed that Chairman Binns was a strong leader and that he challenged the VA to do what was right.

Ms. Julie Mock then spoke for public comment. She stated that in 2005, about 500 veterans came together and spoke of their MS diagnosis. They showed signs of demyelination. The VA staff said yesterday that they did not think this needed to be studied, despite a noted anecdotally increased rate. Ms. Mock has MS and more and more individuals are developing symptoms. Individuals have been dismissed as having a psychological disorder. They are not being provided with proper screening tests. They are not being given the opportunity to have an MRI. Veterans are being dismissed from MS centers of excellence with demyelinating disorders, with their MS characterization being removed, which makes it impossible to receive appropriate care. They were no longer able to receive MS medications to help. She would like clarification from the VA staff as to why they believe it is not necessary to look at MS in Gulf War veterans.

Dr. Davey replied to this question by stating that she thought there was a difference between looking for what she thinks is a request for incidence of MS versus the number of cases that are

present right now. The VA is very concerned with GW veterans and for any veterans that have MS. The VA would always want to provide care for individuals with MS. How we study it in this particular population has been discussed. There are varying themes in how to approach it so that resources are used appropriately. The IOM has recommended that this use of resources would not at this time be the most appropriate. The care of veterans with MS and the amelioration of MS in Gulf War veterans is of utmost importance. There is a plan in action in how to approach that.

Ms. Mock asked whether there was a method of collection for veterans who were showing symptoms of demyelination to inform neurologists within the VA that this could be happening. She asked whether there was a way to informally collect that data. People are becoming sicker, more quickly, and there is a need for information now.

Chairman Binns noted that there was a disconnect between what the VA was classifying as Gulf War research, where they include MS studies, and their failure to conduct research on the incidence of MS in Gulf War veterans, as they've been congressionally mandated to do.

Ms. Denise Nichols spoke for public comment. She thanked the Committee, staff, and researchers. She noted the excellent research in Florida and with Dr. Steele in Texas. She has a renewed hope after this meeting. Especially after Dr. Klimas and Dr. Broderick's presentations, there seems to be new and exciting things that could be ahead. She backed up Ms. Mock's comments on MS research. Any time soldiers go to war, there should be data on mortality, morbidity, what they are experiencing in theater. She does not know where those reports went after the GW veterans arrived home, but they should have been filed and accounted for. She cannot believe that in this day and age, the prevalence rates for illnesses, the data that are needed, are not available. They are not getting anything from primary care physicians about what they are seeing in this population of GW veterans and this was a disservice, because doctors cannot really understand what was really going on if the data are not available.

Mr. Paul Sullivan submitted a formal public comment, which can be found in **Appendix C**. The following is a brief summary of his statement. Mr. Sullivan is a GW veteran, and his comments are made on behalf of the Veterans for Common Sense, a non-profit organization out of Washington, D.C. He thanked the Committee for their continued service. He hoped that the VA would restore the Committee's 2010 charter so that they can once again effectively report to the VA. He believed that even though the VA took away the Committee's ability to comment to them on Federal research, the Committee should still submit these recommendations to Congress directly. The VA taking this ability away was a direct action against the Committee. The Committee should also ask Secretary Shinseki directly, when the VA will respond to any of the recommendations the Committee has made to the VA since 2002. The VA has not responded to date, and Secretary Shinseki has yet to attend a Committee meeting in person.

Mr. Sullivan asked Dr. Jesse to respond in writing to a letter the veterans wrote to him in August 2013. At present, the only communication the VA has with GW veterans appears to be at Committee meetings. The Committee has submitted specific recommendations, and the VA continues to not respond. The veterans have requested some very specific things from the VA, very feasible things, and they ignore them. He supports the conversation regarding the VA consideration of a presumption of service connection for brain cancer due to research. It is troubling that the VA actions towards GW veterans are woefully inadequate, as a Committee member stated yesterday. Research is not being done where it needs to be, information is not being spread amongst VA medical center locations. Treatments vary greatly. From personal experience, he can say that most VA physicians have no idea that GWI is a physical condition associated with toxic exposures based on Committee and IOM work. Most still consider GWI to be psychological in nature. He thanked the Committee again for their service and stated that he remained deeply disappointed in the continuing adverse action of the VA towards the Committee.

Mr. Kirt Love submitted a written document for public comment, which can be found in **Appendix C**. The following is a brief summary of his statement. Mr. Love felt that the VA has been challenging and undermining in their influence over the past Committee meetings. It is unfair that the offices have been able to affect the Committee in this way, without providing good reason. He stated that the VA Gulf War Task Force excluded all advocated parties other than their own people. Mr. Love sees this as a backward-moving return to individual segregation from public representation. He stated that the Committee has pointed out some of these issues, as well as their nonexistent infrastructure or implementation of any valued GW programs. He stated that the VA ignored its own policies and produced reports at random when it best suited them. Mr. Love has had the ability to watch the Committee experience issues from the VA as they seem to reverse progress on themselves. There are a lot of issues that the VA has, and they continue to press those issues onto the Committee. The executives ignore the Committee, when they should allow the Committee to do what it was designed to do. Mr. Love expressed deep disappointment in the VA. He does not favor getting rid of the Committee in favor of letting the VA have control over the issue of GWI and he feels as though the VA does not care what the veterans think.

Following the public comment period, Chairman Binns adjourned the meeting.