Research Advisory Committee on Gulf War Veterans' Illnesses

September 22-23, 2014 Committee Meeting Minutes

Department of Veterans Affairs
Washington, DC

Research Advisory Committee on Gulf War Veterans' Illnesses
Boston University School of Public Health
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I hereby certify the following minutes as being an accurate record of what transpired at the September 22-23, 2014 meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses.

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

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Attendance Record

Members of the Committee
James Binns, Chairman
Roberta White, Scientific Director
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
Linda Chao
Wesson Ashford
William Meggs
Mohamed Abou-Donia

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

VA Office of Public Health
Robert Bossarte
Erin Dursa
Shannon Barth

VA Office of Public and Intergovernmental Affairs
Madhulika Agarwal, Deputy Undersecretary for Health Policy and Services

Secretary of Veterans Affairs Robert McDonald

Acronyms & Abbreviations

AD - axial diffusivity
ALS – Amyotrophic lateral sclerosis
CA - Cornu Amonis
CAM - Complementary and Alternative Medicine
CATI - Computer Assisted Telephone Interviews
CFS – Chronic fatigue syndrome
CGI - Clinical Global Impression
CMI – Chronic multisymptom illness
CRP - C-reactive protein
CPPS - Chronic Pervasive Pain Syndrome
CRPS - chronic regional pain syndrome
CSF – Cerebral spine fluid
CSP – Cooperative Studies Program
DEET - N,N-diethyl-m-toluamide
DMDC - Defense Manpower Data Center
DOD – Department of Defense
DTI – diffusion tensor imaging
DU - depleted uranium
GW – Gulf War
FA - fractional anisotropy
FACA – Federal Advisory Committee Act
FDA - Food & Drug Administration
FIQ - Fibromyalgia Impact Questionnaire
FFS - Flinders Fatigue Scale
FY – Fiscal Year
GFAP - glial fibrillary acidic protein
GM – grey matter
GMPAC – Genomic Medicine Program Advisory Committee
GW – Gulf War
GWI – Gulf War illness
GWV – Gulf War Veterans
HDRS - Hamilton Depression Rating Scale
H&E - Hematoxylin Eosin
HV – hippocampal volume
IBS – Irritable Bowel Syndrome
ICD-9 - International Classification of Diseases-9
ICD-10 - International Classification of Diseases-10
IG – immune globulin
IL-15 - Interleukin-15
IOM – Institute of Medicine
IND - Investigational New Drug
IRB - Institutional Review Board
ISI - Insomnia Severity Index
LDN - Low dose naltrexone

ME - myalgic encephalomyelitis
MRI – Magnetic Resonance Imaging
MS – Multiple sclerosis
MPH – Master of Public Health
MPQ - McGill Pain Questionnaire
MWM - Morris Water Maze
NDI - National Death Index
NGF - Nerve growth factor
NKCC - Na-K-Cl cotransporter
NRAC – National Research Advisory Council
NMDA - N-Methyl-D-aspartate
OPH – Office of Public Health
ORD – Office of Research and Development
PAMP - pathogen associated molecular pattern
PB – Pyridostigmine bromide
PE – physical evaluation
POW – prisoner of war
PQSI - Pittsburgh Quality Sleep Index
QOL - quality of life
RAC – Research Advisory Committee
RD - radial diffusivity
RFA – Request for application
RSD = Reflex Sympathetic Dystrophy
rTMS – Repetitive transcranial magnetic stimulation
SF-36 - Short Form survey 36
SNAC - Structures Neurotoxicant Exposure Checklist
SPM8 - Statistical Parametric Mapping 8
Th1 - T-helper cell 1
Th17 - T-helper cell 17
TSD - Tardive Sympathetic Dysautonomia
TSSA - Tokyo Subway Sarin Attack
UA - urinalysis
US – United States
UTI - urinary tract infection
VA – Veterans' Administration
VAS - Visual Analogue Scale
VHA – Veterans' Health Administration
VAMC – Veterans' Administration Medical Centers
WM – white matter
WRIISC - War Related Illness & Injury Study Center
4T – 4 Tesla

Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses
September 22-23, 2014
(1-800-767-1750; access code 50055#)

Department of Veteran Affairs, 810 Vermont Avenue, Room 230, Washington, DC
(MONDAY ONLY)

Agenda
Monday, September 22, 2014

8:30 – 9:00	**Informal gathering, coffee**	
9:00 – 9:15	**Welcome, introductory remarks**	**Mr. Jim Binns, Chairman** **Res Adv Cmte Gulf War Illnesses**
9:15 – 10:15	**Update of VA OPH research portfolio**	**Dr. Robert Bossarte** **Dr. Erin Dursa** **Dr. Shannon Barth** **VA Office of Public Health**
10:15 –10:30	**Break**	
10:30 - 11:30	**Update of VA ORD Gulf War research Portfolio**	**Dr. Victor Kalasinsky** **Dr. Robert Jaeger** **VA Office of Research and Development**
11:30 – 12:15	**Neuroimaging studies of the effects of low-level sarin exposure on GW veterans**	**Dr. Linda Chao** **San Francisco VAMC**
12:15 - 1:15	**Lunch**	
1:15 - 2:15	**rTMS in GW veterans with chronic pain and Palo Alto WRIISC update**	**Dr. Wesson Ashford** **Palo Alto VA Medical Center**
2:15 – 3:00	**The efficacy of low dose naltrexone and dextromethorphan in treating GW Illness**	**Dr. William Meggs** **East Carolina University**
3:00 – 3:15	**Break**	
3:15 – 4:00	**The efficacy of flupirtine in an animal model of Gulf War Illness**	**Dr. Mohamed Abou-Donia** **Duke University**
4:00 – 5:00	**Recognition of retired/retiring Committee members**	**Dr. Roberta White, Scientific Director** **Res Adv Cmte Gulf War Illnesses**
5:00 – 5:30	**Public comment**	

Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses
September 23, 2014
(1-800-767-1750; access code 50055#)

Department of Veterans Affairs, 2011 Crystal Drive, Suite 150, Arlington, VA
(TUESDAY ONLY)

Agenda
Tuesday, September 23, 2014

8:45 – 9:00	**Informal gathering, coffee**	
9:00 – 10:45	**'How to discussion': GWI Exposure assessment and biomarker development**	**Dr. Kimberly Sullivan, Assoc. Scientific Dir.** **Dr. Nancy Klimas** **Res Adv Cmte Gulf War Illnesses**
10:45 – 11:00	**Break**	
11:00 – 12:00	**'How to discussion:' GWI study recruitment**	**Dr. Beatrice Golomb** **Res Adv Cmte Gulf War Illnesses**
12:00 - 12:30	**Committee Discussion: 'How to manual'**	**Res Adv Cmte Gulf War Illnesses**
12:30 – 1:00	**Public comment**	
1:00	**Adjourn**	

DAY 1

Welcome, introductory remarks
Mr. James Binns, Committee Chair

Chairman Binns opened day 1 of the September 2014 Research Advisory Committee on Gulf War Veterans' Illnesses meeting. He noted that the meeting held great significance as many of the longstanding Committee members were scheduled to rotate off of the Committee at the conclusion of the meeting. He also thanked the veterans who had made the effort to attend the meeting in-person, and those who were attending by phone. He stated that the recently appointed Secretary of Veterans Affairs Robert McDonald would be attending the meeting sometime during the first day of the meeting. Chairman Binns welcomed the researchers present, and noted the exciting potential biomarker presentation that would be made during the meeting. He then asked Dr. White to comment on some developments that had taken place since the release of the Committee Report in the Spring of 2014.

Dr. Roberta White, Scientific Director

Dr. White noted that the Committee had before them copies of the Committee final report now available to the public. Additionally, the journal Cortex invited the Committee members to write and submit a paper summarizing the report. Dr. White stated that she would get in touch with contributing report writers to ask for edits from the co-authors and this work would become part of the peer-reviewed scientific literature on Gulf War Illness.

Update of VA OPH research portfolio

Dr. Robert Bossarte, VA Office of Public Health

Dr. Bossarte began the presentation by thanking the Committee for the invitation to speak and noting that Dr. Erin Dursa and Ms. Shannon Barth would also be making presentations. For the presentation slides of all three Office of Public Health (OPH) presentations, please refer to **Appendix A – Presentation 1**.

Dr. Bossarte briefly covered the epidemiology program at the VA, and explained that the epidemiology program conducts descriptive, observational and analytic studies of cohorts defined by period of service. He then covered the data being used, consisting of survey data and VHA administrative data within the population cohort. The Gulf War Veteran Roster was covered, including a description of the population, size, and data elements. Vital status and cause of death data through 2012 were being collected at the time of this meeting.

With regards to characteristics of GW veterans and GW veterans who used VHA services, about 92% of veterans were male, about 65% of whom were white. Approximately 70% of GW veterans were 60 years of age and older, with between 50-

60% having served in the Army, 20% in the Navy, 10% in the Air Force, and 10-15% in the Marines.

The highest prevalence of ICD-9 Diagnostic Categories of GW veterans and GW-era veterans who were evaluated and compared to each other indicated that about half of the veterans were seen for endocrine & metabolic disorders, mental disorders, nervous system & sense organ disorders, circulatory system disorders, musculoskeletal and connective tissue problems and for symptoms of 'ill-defined conditions'. In contrast, the number of veterans seen for infectious and parasitic diseases, blood disorders, and malignant and benign neoplasms accounted for less than 20% of ICD-9 diagnostic categories in the deployed and non-deployed groups.

Among GW and GW era veterans diagnosed with a malignant neoplasm, GW veterans showed higher rates of the 'other' malignant neoplasm of the skin category accounting for about one quarter of this group. GW era veterans showed higher rates of the malignant neoplasm of the prostate category which accounted for 24% of the group. GW veterans also showed higher rates of malignant neoplasm of the colon and skin accounting for 6% and 5% respectively, while GW era veterans showed higher rates of malignant neoplasm of the trachea, bronchus, and lung at 6% of the group.

GW veterans and GW era veterans also showed differences in diagnoses of diseases of the nervous system and sense organs. Both groups had the same top three diagnostic categories including refraction disorders, hearing loss problems, and other disorders of the ear. However, GW veterans had higher diagnostic rates of organic sleep disorders and migraines when compared to GW era veterans. GW veterans and GW era veterans were relatively similar when compared with rates of the diagnostic code of 'symptoms of ill-defined conditions'. Another difference in symptoms between the groups was that GW veterans had higher rates of symptoms involving the head and neck, while GW era veterans had higher rates of nonspecific findings on examination of the blood.

Dr. Bossarte invited any questions. Mr. Bunker asked whether OPH would be further breaking these data down into GW veteran subgroups. Dr. Bossarte noted that OPH would be doing this, but that given the time between receiving this information and the meeting, this was as detailed as they were able to present at this meeting.

Dr. Erin Dursa, VA Office of Public Health

Dr. Erin Dursa continued the presentation on behalf of OPH, and she presented the Follow-up Study of a National Cohort of Gulf War and Gulf War Era Veterans survey results. The survey population sample included 15,000 deployed Gulf War Veterans and 15,000 non-deployed Gulf War-era veterans. Prior to the Follow-up study, other studies

conducted included the National Health Survey of Persian Gulf War Era Veterans (1995-1997) and the Longitudinal Health Study of Persian Gulf War Era Veterans (2003-2005).

The data collection for the Follow-up survey study took place from May 2012-December 2013. A total of 2,500 veterans were invited to participate in the validation study and 86% of those records were validated. With regards to the results, weights were applied to produce estimates that reflect what would be expected in the entire population of Gulf War and Gulf Era veterans. For the survey results, there was a 50% response rate that was comprised of a 68% mail survey response, 26% web survey response, and a 6% CATI response. Of the survey responders, 79.7% were male. The highest percent of those serving were in the Army with 64.3%, followed by the Air Force and Navy, both at 12.8% and the Marines at 10.1%. Weighted prevalence (with adjusted odds ratios) for self-reported medical conditions in GW veterans versus GW era veterans were discussed. Considering the highest condition prevalence in the table, of GW veterans 43.9% reported chronic multisymptom illness (CMI), 20.3% reported migraine headache, and 20.2% reported gastritis. In comparison, 20.3% of GW era veterans reported CMI, 16.1% reported migraine headache, and 14.2 reported gastritis. In another comparison between GW veterans and GW era veterans with a positive screen of mental health conditions, GW veterans reported higher rates of PTSD at 20.9%, major depressive disorder at 33.5%, other depressive disorder at 48.2% and anxiety disorder at 18.6%. This was in comparison with GW era veterans, who reported 11.5% PTSD, 21.3% major depressive disorder, 40.3% other depressive disorder, and 14.4% other anxiety disorder.

Of those veterans with self-reported CMI at some time in their lives, GW veterans showed higher weighted prevalence of selected symptoms in the past 12 months than their GW era veteran counterparts. She made a note to show the weighted prevalence of symptoms of those who self-reported CMI. The types of symptoms reported were similar, the highlighted ones were those specific to those GW veterans. She looked forward to working with the data in order to better characterize it. The most noticeable differences were seen in unrefreshing sleep, (86.3% GW veteran and 80.3% GW era veteran), headaches (73.1% GW veteran and 65.9% GW era veteran), and trouble finding words (64.8% GW veteran and 58.0% GW era veterans). GW veterans reported a total of 2009 weighted cases of self-reported brain cancer, with GW era veterans reporting 2498 weighted cases. Of those GW Army veterans who self-reported brain cancer, 27 individuals were Khamisiyah exposed, while 984 were not Khamisiyah exposed.

Dr. Sullivan asked about the methods used to reach those weighted percentages noted in the presentation. Dr. Dursa explained that she used bootstrap weighting calibration, proc-survey logistic analysis. The 1995 survey had the self-reported exposure, so Dr. Dursa planned to examine those and compare against the current study. She would be happy to provide the Committee with the weighting methods. Dr. Steele asked about the self-report

proportion sizes, because they were quite large. Dr. Dursa noted that these numbers were run more than once because the numbers were so large, but noted that they were raw, self-report data, not adjusted or medically validated.

Mr. Bunker noted the mortality rates presented, noting that it was important to look very close at where the individuals served in theater, particularly those individuals who were very close to the demolition at Khamisiyah, Iraq. Dr. Dursa determined the exposed and unexposed sarin groups by using the Department of Defense (DOD) previously determined plume exposure estimates. Dr. Klimas asked for a clarification regarding the brain cancer mortality rates discussed. Dr. Dursa noted that the numbers that she presented were from the 2012 self-report survey. She stated that the numbers were very different than the population as a whole and that Shannon Barth would present more information on mortality rates in the next presentation.

Dr. Bossarte noted that the survey was not designed to capture the entire sample. The survey would capture very few persons with brain cancer, for example. Dr. Klimas made the point that chronic fatigue syndrome would also be higher rates in the whole GW veteran population. Dr. Bossarte agreed and again noted the limitation of the survey. Dr. Sullivan asked for confirmation that the numbers displayed were the actual numbers of brain cancer. Dr. Dursa noted that they were weighted based on people who responded affirmatively on the survey and she would be happy to provide the Committee with actual numbers. Dr. Sullivan noted that it would be important to be careful to note who met diagnostic criteria.

Dr. Klimas asked whether they had or used symptom surveys. Dr. Dursa confirmed that they used the 1994 diagnostic scale. She had a call with Dr. Steele regarding how best to diagnose those given the scale. Dr. Steele noted the CMI question was from the umbrella question regarding illnesses and not from individual symptom questions.

Maj Denise Nichols asked two questions. First, if on the next survey, they could ask if the person knows specifically what type of brain cancer that they have. Second, she asked whether they looked at blood cancers. Dr. Dursa said that they did not specifically ask about blood cancers, but they can look at VA data to see if those using the VA had blood cancers. Maj Nichols noted that any others including liver and kidney cancers should also be queried in the surveys. Dr. Dursa noted that in the response section they did ask for a write-in of specific cancers. They will further look at those data moving forward. Mr. Peter Sullivan asked whether the theater those deployed to in the Persian Gulf War was specified. Dr. Dursa noted that they could have been deployed elsewhere. Dr. Sullivan thanked Dr. Dursa for engaging and providing this new survey data to the Committee. Dr. Dursa thanked everyone for the opportunity to speak.

Ms. Shannon Barth, VA Office of Public Health

Shannon Barth, MPH, concluded the OPH presentations with a discussion on her paper entitled, "Neurological and all-cause mortality among U.S. Veterans of the Gulf War: 20-year follow-up". The objectives of this follow-up study included determining the vital status of a cohort of GW and GW Era veterans through 2011, determine the cause of death among GW and GW Era Veterans, compare mortality rates between GW and GW Era Veterans, and determine the association between neurological and other cause-specific deaths and military, exposure, and demographic characteristics. Background was covered including all-cause mortality and a focus on neurological deaths. The cohort was previously followed-up at 2, 7, and 13 years. Dependent variables in the study included all causes of death, disease-related causes, and external causes. Independent variables included demographic and military characteristics, potential nerve gas exposure at Khamisiyah, and potential oil well fire smoke exposure during the war.

Methods involved updating the vital status through December 31, 2011, using National Death Index (NDI) data, determine ICD-9 or ICD-10 cause of death using NDI data, crude mortality rates calculated per 10,000 person years, and cox proportional hazard models used to adjusted rate ratios. Results were covered in terms of underlying causes of death, both disease-related and external. Neurological causes of death considered included brain cancer, Amyotrophic lateral sclerosis (ALS), Multiple sclerosis (MS), and Parkinson's disease. Oil well fire smoke and nerve gas at Khamisiyah exposures among Army GW veterans was examined. Neurological deaths among Army GW exposed groups were considered with regards to the following variables: oil well fire smoke exposed versus not exposed, one day of exposure at Khamisiyah versus not exposed, and two-plus days of exposure at Khamisiyah versus not exposed.

In summary, Dr. Barth explained that research found no difference in mortality risk among GW and GW Era veterans at the 20 year follow-up study. Gulf War veterans had statistically significant lower risk of death due to all disease related causes and infectious diseases compared to Gulf War Era veterans. Gulf War veterans had statistically significantly high risk of death due to motor vehicle accidents compared to Gulf War Era veterans. There was no increased relative risk of death from neurological diseases among Gulf War versus Gulf War Era veterans. Ms. Barth stated that the findings from the thirteen year follow-up that Army Gulf War veterans who were exposed to nerve agents at Khamisiyah (for two or more days) or oil well fire smoke had greater risk of brain cancer are no longer statistically significant at the 20 year follow-up. There was an increased number of brain cancer deaths among non-exposed groups, and an increased number of person-years in the denominator. Ms. Barth then invited any questions.

Dr. Steele asked for Ms. Barth to confirm that the overall death rate was higher for all groups. Ms. Barth noted that there were seven years of additional data to calculate to

account for this. Dr. Sullivan asked Ms. Barth if the control variables were the same during the prior study that had positive results in 2004. Dr. Sullivan asked if Ms. Barth had looked at the different types of lung cancer as well. Ms. Barth noted that they had not, but were planning to compare them. Dr. Klimas asked if another way to look at the data would be that there are a higher number of deaths closer to the exposure. Dr. Bossarte noted that the data presented is different given the time changes, the time effect on mortality may have affected mortality, which will be seen with more detailed and robust analyses moving forward. Dr. Steele noted two time elements, proximity to exposure, and age of individuals at and beyond exposure. Ms. Barth confirmed this, and noted that the data would be stratified by gender moving forward, as she didn't have time to break it down by gender prior to the current meeting. She thanked everyone for their time.

Dr. Robert Bossarte, VA Office of Public Health

Dr. Bossarte concluded the presentation with future planned analysis, summary and discussion. The future planned analyses for clinical and administrative data include routine reporting on patterns of health care utilization and diagnosis among Gulf War and GW Era Veterans. OPH will look to characterize patients with multiple poorly defined symptoms/illnesses and high service utilizations. OPH planned to conduct further cross-sectional and longitudinal Gulf War surveys. They planned to conduct annual updates for leading causes of death among Gulf War and Era Veterans by age group and sex, conduct a medical records validation of neurological mortality, and to create time dependent models of cancer risk. Dr. Bossarte asked if anyone had any questions before he made his concluding remarks.

Dr. White asked about when they are looking at the exposure, whether they have looked at symptoms versus CMI. CMI can express itself differently in different people. Dr. Bossarte noted that this was something they would look at to the extent that symptoms can be examined in the data. There will be some limitations, but they will work with the data they have. Dr. Steele commended the ambitious agenda set by OPH, and noted that it showed a lot of promise for the future especially with continued analyses. She wondered why in the most recent survey they included CAM treatments, but not other treatments. She echoed Dr. White's question, stressing the language used in the surveys moving forward. They may be able to look at previous wave surveys that asked for more than CAM treatment to help inform the data. Dr. Sullivan echoed Dr. Steele's sentiments. She noted the importance of tapping into state cancer registries to help with the collection of data. Dr. Bossarte thanked her and noted that they recognize the importance of this information and the effort that will be put into getting the best information possible. Dr. Steele noted the absence of a variable in the data presented with regards to differentiating between the specific eras spent or time windows for veterans. She wondered how they

were able to parse this information into these specific areas. Dr. Bossarte explained that they worked to be able to as closely identify these eras and time frames by taking the data they were working with and comparing against/link to the GW roster available, which helped to inform these data in a more specific manner.

Chairman Binns added his thanks to the open approach that was used by OPH to try and analyze the survey data. He recognized the limitations Dr. Bossarte has been working with, and noted that these information gaps in the survey were ignored by prior OPH administrators despite recommendations by the Committee, and that now Dr. Bossarte unfortunately had to work with these data limitations. He also noted that there were major limitations in using data from past diagnoses in VA facilities, given that VA doctors were historically trained to consider Gulf War illness psychosomatic.

Dr. Bossarte noted a few points. He recognized limitations, and appreciated the help provided to help fill those gaps by Committee members. He stated that feedback was incredibly important in getting the information needed. Dr. Bossarte and OPH are moving towards a better, fuller analyses of data over time. They were working towards a set of common core data elements for epidemiology surveys, which could allow for a more thorough, comprehensive, and effective collection of data to be analyzed over time.

With regards to summary and discussion, the Epidemiology Program has proposed to bring together an expert panel to develop recommendations for a common core of elements for sponsored studies. OPH has additionally continued efforts to identify a mechanism that would satisfy legislative requirements for a study of MS and other neurologic disorders among Gulf War Veterans. Some of the questions that OPH would like to get feedback on included: Would a quarterly report of GW Veteran Diagnoses and Healthcare Utilization contribute to research? If so, are there other elements that should be added? Are there other research priorities that can be addressed using clinical or administrative data? Are there other studies of CMI that should be prioritized using available data? Are there other studies of cancer (particularly brain cancer) that should be considered? Should VA studies of cancer incidence include data from available state registries or should they be limited to information available from VA? Should there be a fourth wave of the GW Survey?

Dr. Steele noted the comprehensive list of all data sets in the VA strategic plan that might be of benefit. She also noted that if the last wave of the survey included questions about neurological diseases, it is probably one of the best surveys and data sets gathered to date. Dr. Bossarte thanked her, and noted that they would be more than happy to make any available gathered (including IOM study) that they have access to available to the Committee. Dr. Sullivan asked whether there was a plan to do a Pre-9/11 GW health utilization report (formerly Gulf War Veterans Information System, GWVIS) again. Dr.

Bossarte noted that they would be looking to do an update on the report and that it will look different than the original report, but will provide new information.

Update of VA ORD Gulf War Research Portfolio
Dr. Victor Kalasinsky, VA Office of Research and Development

Dr. Kalasinsky of the Office of Research and Development (ORD) began by thanking the Research Advisory Committee, members of the VA, and the audience for being present for the meeting. VA research is driven to improve the health care for all Veterans, through investigator-initiated research (clinician researchers), service-directed research, and the Cooperative Studies Program (CSP). There are a number of sites accessible by the public where they can access information about VA/ORD funded research (sites available on slides, **Appendix A - Presentation 2)**.

There were a total of six Gulf War Research Requests for Applications (RFAs) across biomedical laboratory R&D, clinical science R&D, and health services R&D since the last Committee meeting. The Gulf War Research Strategic Plan (2013-2017) was briefly covered, with attention on the eight focus areas. Response statistics for VA-ORD Gulf War research RFAs in Spring of 2014 included a total of eighteen proposals received and two projects funded for a total of $2.3 million dollars in funds approved. There were 29 Gulf War Research projects active in 2014, which span the eight focus areas of the Research Strategic Plan. There were an additional four Gulf War Research projects selected for funding in 2014. Eight Gulf War Research projects were completed in FY 2013, from which publications would follow.

Dr. Kalasinsky discussed the two Gulf War Research Biorepositories, CSP #585 Gulf War Era Cohort and Repository, and the Gulf War Veterans' Illnesses Biorepository. Gulf War Research Activities have included the Institute of Medicine (IOM) Case Definition of Chronic Multisymptom Illness in 1990-1991 Gulf War Veterans, the Mitochondrial Disease conference held in June 2014, and the Gulf War Veterans Outreach program that was conducted.

Dr. Sullivan asked when the biorepositories would be transitioned from the pilot phase to the fully funded phase of the studies. Dr. Kalasinsky stated that once the preliminary numbers were gathered, they would begin recruiting to increase the tissues, and data samples in the biorepositories. Dr. Timothy O'Leary (Chief Research and Development Officer) commented that the group needed to consider what was and was not working in the biorepository studies. When large studies are budgeted, the actual costs often vary considerably from actual budgets. Study design in the pilot would be adjusted according to these variances. It was likely that recommendations in terms of other approaches to outreach to Gulf War Veterans would absolutely be helpful. Dr. Sullivan thanked him

and noted that recruitment strategies to date are outdated and limited, so she was glad to see that input would be accepted. Dr. O'Leary agreed, noting the importance of the Committee in providing suggestions.

Dr. Golomb asked a question about slide 10 presented by Dr. Kalasinsky regarding Gulf War research funding. She noted the ongoing concerns of the RAC were the topic matter of the projects funded under Gulf War research funds. She stated that a number of those projects were not directly related to Gulf War research, specifically in groups that are not Gulf War veterans. Dr. Kalasinsky replied that they are projects that inform problems faced by Gulf War veterans. Dr. Golomb noted that GW veterans are not immune to any problem, and that the funding really needs to be targeted toward the chronic multisymptom illness condition that is specific to Gulf War veterans. Dr. Golomb noted the sleep apnea study, noting that this was a condition that the whole population of veterans present with, and was not specific to Gulf War veterans. Gulf War funding should be directed specifically towards research pertaining to Gulf War veterans. Dr. O'Leary noted that no Gulf War project that met the criteria for funding by ORD has been denied funding, so long as it was deemed to have met all the criteria. Dr. Kalasinsky added that they make sure that they fund the right studies that will help Gulf War illness.

Dr. Sullivan asked Dr. Kalasinsky for updated abstracts on studies funded through the GW research program, Dr. Kalasinsky said he would provide them. Dr. Steele agreed with Dr. Golomb that some of these studies in some ways "pad" the portfolio, but that moving forward it would be in the best interest of the VA to ensure that the studies funded are directly related to Gulf War veterans and GWI. Dr. Klimas asked whether there was a plan in the cooperative study CSP 585 study to survey GW era veterans with the same survey instrument. Dr. Kalasinsky noted that this study includes the same questions, and same amount of blood being collected in all groups. Somewhere in the range of 10-12% of the samples are veterans who were in the military during the Gulf War. Dr. O'Leary noted that there is self-reported information in the survey that is probably not enough alone to look for Gulf War illness in a veteran, but combined with other information might be enough to inform a study with Gulf War veterans. The use of the roster was still to some extent under the control of the DOD, but Dr. O'Leary stressed that they were making efforts to be able to get full access to it.

Dr. Steele asked about criterion scores, and why proposed studies that were achieving good scores were not being funded at a certain score where other studies typically are. Dr. O'Leary reported that many of these borderline scores had some methodology issues, where changes needed to be made to reflect a better methodology for the study to be funded. Dr. Kalasinsky added that his office was actively trying to recruit researchers who have experience working with Gulf War veterans and in Gulf War research. ORD

provides feedback to applications that do not pass review for funding, and get in touch with these researchers to try and work with them so that they can resubmit and receive the funding for the research they would like to do.
Dr. Fiona Crawford asked whether there were plans for the funding criteria to change for those who are not VA researchers, who are currently ineligible to participate in the research. Dr. Kalasinsky stated that there are some constrictions they unfortunately cannot work around. Dr. Crawford noted that those who are partly funded but are still under eligibility criteria should be able to participate. Dr. O'Leary said that he could look at specific issues, but some things are considered when looking to become eligible for funding. This is an area of research where they would look more positively on deeming an individual researcher eligible to VA funding. Dr. O'Leary committed to looking back at those individuals who have gone through efforts to become eligible but have been unable to, and will report back to the Committee. Dr. Klimas noted the point that it is difficult for researchers to even figure out what they need to apply to be a VA investigator. Dr. O'Leary noted positively that Secretary McDonald has been making a number of presentations at medical schools to try and recruit students and new physicians to drive greater interest in clinician researchers.

Chairman Binns noted Dr. Kalasinsky's slide with the title "CSP-585 Gulf War Era Biorepository". He wanted to make a note that the term 'Gulf War Era' was often associated with the longer Gulf War duration (1990-2014). Dr. Kalasinsky noted that this was not the case in his slide and that it represented those in the military in 1990-1991. Chairman Binns asked that they specify this better in future presentations. Dr. Kalasinsky noted that there was no program in ORD that is more flexible than the GW program with regards to eligibility criteria and it might be important to consider taking up questions with the specific medical center where these issues arise.

Dr. Kalasinsky stated that with regards to coordination between the VA and the Department of Defense, there have been regular briefings and updates between the Gulf War Program Managers at ORD and the CDMRP GW research programs. He also noted there was a periodic review of proposals submitted and funded between the agencies and there were CDMRP briefings to the RAC Committee. The VA produces a joint Annual Report to Congress in collaboration with the CDMRP GWI program. He concluded the presentation and thanked everyone for their time.

Chairman Binns noted that the 2010 IOM report found an association between chronic multisymptom illness (Gulf War Illness) and service in the Gulf War. He asked whether CMI would be service connected as a result. Dr. Fred Florin of the Veterans Benefits Administration commented that CMI and undiagnosed illness are presumptive for veterans of the first Gulf War. Dr. Golomb stated that as a VA physician, she has seen

veterans almost universally denied benefits and that the express change in language has not changed the behavior. James Bunker noted that the veteran service organizations (VSO's) need to make a point to clarify this language and that the change needs to be submitted with paperwork to make it clear.

Dr. Florin added that as a part of an ongoing GW task force, they have been actively tasked to make sure this language is clear and disseminated properly. Chairman Binns noted that the latest study finding that about 40% of GW veterans suffer from Gulf War illness. This means almost 280,000 individuals. To date, however, just over 11,000 GW veterans have been approved in the claims filed, with 80% of claims being denied. Dr. Florin noted that this has been a very difficult disease to diagnose, when diagnoses are provided, to prove that this is in fact service connected, is very difficult. VA has been trying to rectify those gaps. As of June, 22,000 veterans had been connected to service with their claims. Chairman Binns noted that there was a large gap between the data reported that morning by the OPH and those numbers just reported. Dr. Florin noted that there were differences in claims data and number of people treated that accounted for the differences.

Dr. Sullivan asked whether ORD was considering taking the IOM recommendation that VA use the term "Gulf War Illness" in their text of the strategic plan going forward since the RAC Committee had also made the recommendation many times. She also noted that a consideration moving forward for VA could be to start utilizing the treatments from trials that have reported positive findings. Dr. Kalasinsky noted that his office has been trying to talk with researchers about increasing the number of small clinical treatment trials. Dr. O'Leary noted this program was called the CTTA, a small clinical trials program enhanced by the fact that they have a much higher level of coordination with VA pharmacy staff and a number of other resources. Dr. Sullivan noted the importance of pushing initial positive findings forward and with getting treatment trials off the ground quicker. Dr. Kalasinsky thanked everyone for their time.

Neuroimaging studies of the effects of low-level sarin exposure on GW veterans
Dr. Linda Chao, San Francisco VAMC

Dr. Linda Chao of the San Francisco Veterans' Administration Medical Center (VAMC) presented her neuroimaging studies of the effects of low-level sarin exposure on GW veterans. For slides, please refer to **Appendix A – Presentation 3**. Background on the United States (US) troops in Khamisiyah, Iraq was provided, detailing the ammunitions storage complexes destroyed by US troops that resulted in the release of sarin nerve gas into the air. Model images of the potential hazard area at Khamisiyah were displayed, from days one to four of the pit demolitions in March 1991.

Dr. Chao described the 1.5 Tesla MRI study sample, which 279 Gulf War veterans were studied between 2002-2007. Exposed veterans were matched demographically to non-exposed veterans. In the magnetic resonance imaging (MRI) analyses, cortical gray matter (GM), white matter (WM), and cerebral spinal fluid (CSF) were measured. Results of the MRI study showed that exposed veterans had smaller total brain GM volume than unexposed veterans.

Dr. Chao discussed the 1995 Tokyo subway sarin attack, noting the affects that sarin poisoning had on the hippocampus and brain structural changes in the victims. MRI results of the GW veteran study similarly showed that exposed veterans had smaller hippocampal volumes (HV) than unexposed veterans. Dr. Chao and her team conducted a follow-up study with more subjects imaged at a higher magnetic field strength to determine if they could replicate previous findings with a 4 Tesla (4T) magnet study. The 4T MRI results showed that exposed veterans had smaller total brain GM and WM volume and larger CSF volume compared to unexposed veterans. Dr. Chao also used diffusion tensor imaging (DTI) to quantify the microstructural integrity of the WM tracks in the brain. DTI results showed lower fractional anisotropy (FA) values indicating reduced microstructural integrity of the WM tracks in the veterans. The DTI results also showed higher axial diffusivity (AD) values indicating greater axonal degeneration in the exposed GW veterans. The DTI results also showed higher radial diffusivity (RD) indicating demyelination and neuroinflammation. Dr. Chao summarized the results as showing that low-level sarin and cyclosarin exposure had an effect on GM volume, WM volume, and WM integrity in exposed veterans.

Dr. Chao then examined the effects that exposure to sarin and cyclosarin on neurobehavioral function. She explained that the Tokyo Subway Sarin Attack (TSSA) victims experienced both impaired memory and psychomotor function. Compared with research conducted by Dr. Roberta White and Dr. Susan Proctor's group at Boston University, deployed Gulf War veterans who self-reported chemical exposure while in theater experienced impaired psychomotor, memory and visuospatial function. Dr. Chao reported that the exposed group performed worse on a measure of verbal memory (California Verbal Learning Test) which she indicated was in line with the previously described tests on neurobehavioral/cognitive function and showed that low-level sarin/cyclosarin exposure has an effect on memory, psychomotor function, visuospatial ability, and attention.

Dr. Chao discussed potential future avenues of her research including whether there is on-going GM and WM atrophy and insult to WM integrity in exposed GW veterans and whether this will result in accelerated aging and neurodegenerative diseases in exposed veterans. She also discussed whether there may be therapies that could slow or reverse these effects. She then asked for questions from the Committee.

Dr. O'Callaghan asked for the criteria used to collect the study data. Dr. Chao received the list of all GW veterans who lived on the West Coast from the Department of Defense's DMDC (Defense Manpower Data Center) lists. She then submitted the list to the defense health headquarters, who cross checked the list with those who had the sarin exposure. Dr. White then noted that the research group in Boston thought that the cognitive issues seen in sarin exposed GW veterans was important to look at because these issues reflected diminished integrity of the white matter. The working memory problems, attention problems, language problems, and visuospatial problems were all indicative of this pattern, while language was intact. This was how the Boston group became interested in studying WM with MRI.

She wanted to follow on with two interesting points by Dr. Chao. First, there was the issue of GWI, and then there was sarin exposure related changes in the brain, which are not necessarily a one to one overlapping thing. Gulf War veterans have a much more complex picture of health than simply GWI or no GWI. There may be GW veterans who have GWI and also neurological issues but that may not be Gulf-War related, and this is a very important difference to note. She noted that they controlled in their study for exposed or not exposed to sarin. Dr. White also noted that it makes her nervous when effects are seen only in one hemisphere of the brain; she asked if they had a hypothesis for this. Dr. Chao noted that she did not currently have a hypothesis for this finding. She noted that at the lower statistical confidence level that the results were seen in both hemispheres, but at stronger statistical significance levels, they were seen only in one hemisphere. She stated that the study results needed to be replicated in more subjects, which was ongoing.

Dr. Golomb asked whether adjustment for CMI might represent an overcorrection, and whether the Khamisiyah exposed group had higher rates of CMI, and whether those findings are magnified in this group. Dr. Chao found that in the first two studies, they did not have the best methods to quantify CMI. Data on severity was not seen. On the new study, they were using Dr. Steele's questionnaire, so she hopes to be able to better stratify the data for GWI case criteria. However, she stated that there was not higher incidence of CMI in one group or another in the studies shown. Dr. Steele noted the importance of comparing the data with that of the Tokyo subway attack study and Dr. White's GW veteran papers, because these basically took CMI out of the equation. She asked though, if in one of the earlier studies, there was greater effect with CMI. Dr. Chao noted that there was greater effect in grey matter, but they'll see if they can replicate that in her current study. Dr. Steele asked if they were looking at other exposures as well. Dr. Chao is looking in the current study at the other exposures to try and further compare the data. Dr. Sullivan thanked her for the presentation, and noted the studies being conducted and

the similar results they are seeing. The longitudinal data they will be looking at will be very important too. Dr. Chao noted that they will be using the 3-Tesla imaging on the current study. Dr. Sullivan noted the importance to differentiate between the scanner strengths in the studies.

rTMS in GW veterans with chronic pain and Palo Alto WRIISC update
Dr. Wesson Ashford, Palo Alto VA Medical Center

Dr. Wesson Ashford from the War Related Illness & Injury Study Center (WRIISC) presented on treating pain in Gulf War Illness with transcranial magnetic stimulation and other methods. For presentation slides, please refer to **Appendix A – Presentation 4**. The WRIISC approached the treatment of pain through a number of different avenues: the WRIISC experience, understanding Chronic Multisymptom Illness (CMI), Tardive Sympathetic Dysautonomia (TSD), symptoms explained, pain causation, management of pain, and research through WRIISC projects. A brief background on the WRIISC was provided, including its founding, mission, service areas, and veterans served. Dr. Ashford discussed symptoms of affected Gulf War veterans and their prevalence through the VA Registry (1992-1997) and the Iowa Study. Of those Gulf War veterans being referred to the WRIISC, the largest symptom experienced had been pain related. The top three symptoms of veterans presenting to the WRIISC program in the last year have been pain, mental health, and cognitive complaints. The affected bodily systems in Gulf War veterans are musculoskeletal, gastrointestinal, respiratory, neurologic, mood and cognitive, fatigue and skin related. Dr. Ashford asked what all of the systems had in common.

Fundamental problems in the Gulf War illness arena include that while “Gulf War illness” is considered to exist per IOM 2010 report, there is no recognized “Gulf War Syndrome”. Additionally, CMI provides no indication of the nature of the condition; there have been many explanations considered, but none have yielded an acceptable explanation. The potential Operation Desert Shield/Desert Storm exposure concerns were highlighted, in addition to the numerous IOM studies and reports on Gulf War illness. Findings included that Gulf War illness is no previously identified diagnostic entity. He stated that some of the possible causes of GWI are cholinesterase inhibitors, other chemical exposures, infectious diseases, multiple vaccinations, depleted uranium, and aspartame/methanol poisoning. Dr. Ashford explained the example of a possible explanation for Gulf War illness as Idiopathic Small Fiber Neuropathy. There was also the anti-cholinesterase withdrawal hypothesis, the acetylcholinesterase inhibitor exposure is the factor most closely associated with Gulf War illness. Tardive Sympathetic Dysautonomia (TSD) was also examined, commonly seen in fibromyalgia, chronic fatigue syndrome, and irritable bowel syndrome. TSD occurs late in Gulf War veterans,

usually after their return. Nerve growth factor (NGF) stimulates the outgrowth of sympathetic ganglion fibers, NGF injections are related to chronic pain syndromes.

Dr. Ashford considered the chronic pain syndromes, including chronic regional pain syndrome (CRPS); Type 1 CRPS is Reflex Sympathetic Dystrophy (RSD). Chronic Pervasive Pain Syndrome (CPPS) is the additional syndrome, which includes TSD. Possible treatments for pain and other Gulf War illness symptoms are varied. The pharmacologic route includes avoiding narcotics, tranquilizers, central anti-cholinergics, considering anti-depressants with anti-pain effects, cholinergic agents, and numerous adrenergic agents. There was the non-pharmacologic approach, which includes low-impact, non-exhausting, graded exercise. New approaches considered include noninvasive brain stimulation with repetitive transcranial magnetic stimulation (rTMS), and Complementary and Alternative Medicine (CAM). A number of primary care, Gulf War illness, and VA resources were covered, in addition to the condition/symptom specific treatment recommendations from the 2001 IOM Report. The treatment recommendations from the 2013 IOM Report added the additional focus on CMI. The focus on the diagnosis and treatment development for GWI Veterans was highlighted, listing the currently funded studies, and proposed studies moving forward.

Dr. Ashford then described his first funded study to examine rTMS for the treatment of chronic pain in GW veterans. rTMS treatment is a method of non-invasive brain stimulation that is done on an outpatient basis. Research shows that rTMS can reduce fibromyalgia pain in patients. Other benefits shown of this treatment in fibromyalgia include improved general activity, relationships with other people, enjoyment of life, morning tiredness, sleep, fatigue, walking, and stiffness. The aim of the study conducted was to determine whether repetitive rTMS would benefit the symptoms of chronic pain in GWI veterans. A brief pain inventory was conducted, and treatment effects were shown on the average patient, active treatment versus sham treatment. Other outcome measures were examined, including Pittsburgh Quality Sleep Index (PQSI), Flinders Fatigue Scale (FFS), Fibromyalgia Impact Questionnaire (FIQ), Insomnia Severity Index (ISI), McGill Pain Questionnaire (MPQ), and the Hamilton Depression Rating Scale (HDRS). Dr. Ashford asked all present in the room to help find Gulf War veterans to participate who have chronic pain and can get to the VA Palo Alto for 20 treatments.

Dr. Ashford provided an introduction to the yoga research project recently funded at the Palo Alto WRIISC, with current research suggesting that yoga may be effective for treating chronic pain. No studies had yet examined the benefits of yoga for treating pain in GWI. The current research is a multimodal evaluation of the comparative efficacy of yoga versus a patient-centered support group for treating chronic pain in GWI. The treatment design is 24 weeks total, with 50 individuals per group. The primary outcome measure was pain, with secondary outcome measures including quality of life (QOL),

fatigue, medication use, mood, and autonomic nervous system function. The study design involved participants being treated one day per week for ten weeks. Dr. Ashford provided contact information for the studies (please see **Appendix A – Presentation 4**), and thanked the Committee for the opportunity to present. He then fielded any questions from members.

Dr. Klimas asked how in the data sympathetic dysautonomia was not postural orthostatic tachycardia syndrome (POTS). Dr. Ashford noted that POTS was not his area of expertise, it was his colleague's Dr. Chang. Dr. Klimas noted the use of exercise, in which veterans will collapse if over-exercised. She noted the need to know what capacity is for these individuals. In a swimming study, people would drop out of the study very quickly. Dr. Ashford did not disagree with what she was saying; he was trying to think of ways to devise safe exercising in a gradual way. Getting individuals in the water for very short, low intensity periods a few times a week, could be of great benefit to the veterans. Dr. Klimas thought that these explicit directions should be provided to physical therapists, making sure they know what the healthy workout for a GW veteran was. Dr. Ashford had a lot of veterans talk about the issues they had with exercise, and saw swimming as a way to slowly start a reconditioning program. Mr. Bunker noted the excellent job that the WRIISC center had done with helping to improve veterans' health.

Dr. White noted that the hypothesis was interesting, especially since he paid a lot of attention to the autonomic nervous system. She noted that literature implicates the autonomic nervous system, the central nervous system, and exposures having implications in GWI. Delayed effects on both systems were very common with chronic low dose toxicant exposures. Dr. Ashford noted that the question about change in thickness of the brain matter could be related to effects of a number of things. Dr. White noted that chemicals are designed to contact the brain, and white matter findings are seen in CMI and non-CMI patients as well. She also noted the data on current rates of depression, anxiety and PTSD. She can say that the rates of those conditions were much lower than that. With the Ft. Devens Cohort, they will be looking at some of these mental health issue trajectories. GWI itself has a number of mental health implications; this is not something that should be lost sight of. Dr. Ashford discussed the need to focus the attention on the autonomic nervous system, potentially in line with the central nervous system, to try and help the veterans. Dr. Sullivan agreed, and noted the importance of the combination of exposures that the veterans have faced.

Dr. Golomb agreed that it is important to look at the autonomic nervous system. She also noted the importance of looking at oxidative stress and mitochondrial dysfunction. New evidence showed that oxidative stress is altered significantly in GW veterans. She noted that squalene was not approved in the US. Just because it is in people, does not mean that

it needs to be ejected. Although PB does not cross the blood/brain barrier in large numbers, a number of others do. Dr. Sullivan noted the other area of GWI is neuroinflammation. There is a write-up of work on this available to the Committee members in the binder. Dr. Ashford noted that the reaction could potentially be a lack of response of neurons; it also could be an over-response of neurons. Dr. Sullivan noted the importance of his work, and in the areas he was looking at specifically to treat veterans. Dr. Ashford thanked everyone for their time.

The efficacy of low dose naltrexone and dextromethorphan in treating GW Illness
Dr. William Meggs, East Carolina University

Dr. William Meggs presented on the trial of naltrexone & dextromethorphan for Gulf War Illness. For presentation slides, please refer to **Appendix A – Presentation 5.** The hypothesis the trial worked on was that GWI is an inflammatory cycle involving the brain, it may be a common mechanism of many neurological conditions, and asked whether it was initiated by toxic exposures, infection, or trauma. Previous studies suggest that novel anti-inflammatory drugs may be of benefit in symptom-defined illnesses related to neuroinflammation. Morphine-related analogs, including naltrexone and dextromethorphan may provide anti-inflammation and neuro-protective effects. Naltrexone HCl is a generic drug with Food & Drug Administration (FDA) approved indications in alcohol and opioid dependence, and a non-FDA approved indication in drug withdrawal. Some adverse effects include asymptomatic elevations of hepatic transaminases, liver dysfunction, dizziness, headache, insomnia, and somnolence.

Low dose naltrexone (LDN) has been tested in Crohn's disease, multiple sclerosis, cancer-related pain, fibromyalgia, and chronic low back pain. Studies in Crohn's Disease suggest that LDN therapy appears effective and safe in subjects with active Crohn's disease, but further studies are needed to explore the use of this compound. Dextromethorphan is generic and available over the counter. It has been used as a cough suppressant. The Institutional Review Board (IRB) approval for the study was challenging. Reasons for the challenges included slow turnaround, Investigational New Drug (IND) applications, need for the modification of the case definition, and need for the modification of the protocol.

The three-arm randomized, double-blinded trial protocol was eleven months in duration, on a course of dextromethorphan, naltrexone, or placebo (three months on, one month off, three on, one off, three on). The naltrexone randomized, double-blinded trial was for veterans taking anti-depressants but no opioids. The participants were provided with naltrexone or a placebo (three months on, one month off, three months on). The dextromethorphan only randomized, double-blinded trial was for veterans with chronic opioid therapy but no antidepressant use. The participants were provided with either

dextromethorphan or a placebo (three months on, one month off, three months on). Recruitment and screening criteria were both discussed, including locations of recruitment and screening instruments utilized. Clinical evaluations of recruits included a history and physical exam, visual analogue scale, clinical global impression scale, Short Form survey 36 (SF-36), and Connor's continuous performance test (CPT). Laboratory evaluations included the routine complete blood count, comprehensive metabolic profile, and urinalysis (UA). Research evaluations included C-reactive protein (CRP), nerve growth factor, and cytokine/chemokine panels.

A total of 38 men and three women participated in the study, with a mean age of 53 years, spread across the Army, Marine Corp, and Navy branches of service. A variety of psychotropic, seizure, analgesic, and anti-inflammatory medications were being used by participants to treat symptoms of GWI. Participants were given physical examinations, with considerable findings in muscle and joint tenderness, overweightness, abnormal upper respiratory examinations, and decreased vibratory sense. Visual Analogue Scale (VAS) scores for sleeping problems significantly decreased with both naltrexone, dextromethorphan, and their respective placebos. A positive finding was found for VAS scores for concentration problems, with significantly decreased problems using dextromethorphan but not its placebo. Additionally, VAS scores with dextromethorphan alone for memory problems were significantly better than its placebo. VAS scores for fatigue were significantly affected with dextromethorphan but not its placebo. For pain, no effects were found for either drug. Muscle aches were significantly decreased with dextromethorphan but not its placebo. Scores for inappropriate anger found an effect with naltrexone and its placebo, no effect with dextromethorphan or its placebo. Clinical Global Impression (CGI) scores significantly increased over baseline with naltrexone or its placebo. CGI scores also significantly increased over baseline with dextromethorphan and its placebo, but the dextromethorphan placebo scores are significantly lower than the dextromethorphan scores alone.

Confounders in the study included acute illness, small bowel obstruction, pneumonia, or sinusitis. Dr. Meggs also described the beneficial effects he has witnessed with his participants participating in dietary elimination of sugar, caffeine, gluten, and dairy, which promoted significant weight loss, and an improvement of common symptoms when done in line with the treatment. Limitations included no pharmacokinetic data, no normal controls for NGF and human cytokine/chemokine panels, snap shot limitation, and concurrent treatments. Preliminary conclusions were varied. At the doses used, there were responders and non-responders. There was no statistical benefit on the treatment when averaged over all participants. The NGF and cytokine panel data showed no consistent pattern of variability. Empirical pharmacology treatments demonstrated no benefits relative to those using no medications. Things to consider moving forward would be to make sure adequate time is allowed for IRB and FDA approvals, to adjust doses

using pharmacokinetic data, to conduct weekly VAS rather than pre- and post-symptoms scores, and to record VAS scores after discontinuation of the medication.

Dr. Meggs thanked the Committee for their time, and invited questions. Dr. Klimas asked if the study referred to was still going on at the time of the meeting. Dr. Meggs noted that this was the case, recruitment was about half of the total recruitment numbers they wanted to see. Dr. Klimas asked a question about dosing, she wondered whether the dose was very high, as it seemed like it was to her. She heard from a colleague that the dosing doesn't matter so much as the time of dosing, and she wondered if this was considered. Dr. Meggs noted that the time of dosing did not matter for effect, but participants dosed typically in the morning. The dose was recommended to him prior to the study as the standard dose. Dr. Klimas noted a prolonged effect of certain treatments after they stop dosing. Dr. Meggs looked for crossover effects in treatments, in change from beginning of naltrexone to the end, and beginning of dextromethorphan to the end. They can look for ordering and changes across treatment. Dr. Steele noted that crossover designs are important and she is very glad Dr. Meggs was working on that.

Comments of Secretary Robert McDonald

Chairman Binns introduced Secretary of Veterans Affairs Robert McDonald, welcoming him to the Research Advisory Committee meeting. He thanked everyone for the opportunity to be present. Secretary McDonald said that this has been an area that he has really tried to dive into to learn as much as possible, having read as much as he could leading up to this meeting. He asked whether he could hear one or two points from each of the Committee members about their thoughts on where he should focus going forward with GW research.

Dr. White suggested that VA should pursue treatment trials as aggressively as possible, and to work to create definitive diagnostic criteria for Gulf War illness. That could include biomarkers, exposures, and symptoms. Secretary McDonald noted that he read through the literature on treatment options. He asked about the different potential causes, that could result in different symptoms, and different treatments. He asked whether PB pills were still considered causative. Dr. White replied that they definitely still were, just that there had not been updates on research on those since then. Vaccines are something the Committee is less sure about with regards to causality. Secretary McDonald asked about treatments specifically. Dr. White says to consider the cause, but then the mechanism of Gulf War illness. Veterans were exposed to a mixture of chemicals that promoted a number of mechanisms, which cause the symptoms. The treatment targets could be symptom relief, but the most promising researchers are trying to focus on the underlying mechanisms of the disease to develop therapeutic treatment.

Dr. Sullivan thanked Secretary McDonald for attending the meeting. She would like for physicians to be educated on Gulf War illness and treatment options; this information is not being properly disseminated to VA clinicians. Secretary McDonald asked Dr. Agarwal at the VA how they trained physicians currently. Dr. Agarwal noted that they have two experts present at the meeting. Three centers of excellence, called the WRIISC centers. Education is one of the primary pillars of the centers. Dr. Agarwal has tasked these centers to educate and disseminate among other VA medical centers. Dr. Sullivan noted that there has got to be a way to get this information to non-WRIISC physicians, because it is not being done so currently. Dr. Sullivan's second point was to have Sec. McDonald peruse the meeting minutes of past meetings, because there have been a number of great scientists presenting at these meetings. Chairman Binns noted Dr. Abou-Donia's cutting edge research on a possible biomarker test for Gulf War Illness, which he would be presenting at this meeting.

Dr. Klimas noted that with regards to aging, VA should be focusing on neuroprotective agents with GWI to help protect against neuroinflammation. Being able to repurpose drugs or look at pipeline drugs is important. VA needs to be able to rapidly deploy phase I and II studies to be able to find treatments for GWI as quickly as possible. Setting up the mechanism of a clinical trials group, and then determining those drugs that require aggressive push, she believes is the best way to deliver on this issue. Dr. Klimas also noted the high need to educate. Very few physicians know about how to diagnose let alone treat Gulf War illness. Create a training program, but go beyond lectures. Identify those people that need to be trained, have an expert at every site. Without an identified expert at every facility, nothing will change.

Dr. Steele's first suggestion would be for VA to acknowledge that there is a problem. Many veterans are still told by their local VA that GWI is not a real problem. The VA has never explicitly come out and stated in public that this is a real illness, and that it needs to be acknowledged. The second recommendation would be the urgent need for treatments. She suggested some kind of a very well organized center of excellence to identify and develop treatments from beginning to end would be the most effective.

Dr. O'Callaghan endorsed Dr. Steele's comment on the development of collaborative centers where drugs can be developed through lab and into the population. Larger consortiums or centers of excellence will be of huge benefit especially in being able to provide multiple viewpoints. He would also like to see a push for treatment with the implications it could have on not only Gulf War veterans, but in veterans moving forward and also the larger population of individuals.

Dr. Fiona Crawford echoed the importance of education and ensuring that people are able to get quality care at their VA without having to travel very far to an out of state VA for any treatment. She also echoed the need to ramp up clinical trials, getting as many as possible so that they can be ruled out or advanced as soon as possible. It is important to bring the experts to the table so that the people who have the proper expertise can move forward and carry out the needed steps bringing drugs to treatment for patients.

She also commented that she thinks it is very important that the RAC continues, and that the senior members of the RAC should remain. Secretary McDonald commented on Dr. Crawford's final recommendation. He noted that membership rotation has been uneven. His intention would be to follow term-limits, but also to be as inclusive as possible, so that people not currently on the Committee can have an impact on what happens. He would like to figure out how to use different agencies to create a larger social impact, to better publicize GWI. Dr. Crawford noted that his points were well taken. Bringing people together to make it a global issue is a very important action to take. Dr. White noted that a number of nations outside of the US all acknowledge Gulf War Illness, despite the US having the largest research base.

Mr. Bunker noted that a lot of the CDMRP research should be examined, because a lot of it shows promise. Small studies are not being followed up. Mr. Bunker also noted the high number of claims denials that have occurred. Fixing the VA and the holes in Gulf War claims would do the best service for veterans.

Dr. Golomb reiterated comments made by Committee members. There should be a training module that would be required, because many VA medical centers still carry the idea that GWI is not a real illness, that it is still a mental issue. She wanted to suggest a veteran integration panel by GW veterans that helps to suggest which research should be funded by a relevancy standpoint. Dr. Klimas noted that it would be very beneficial if VA could put together some sort of conference to gather experts in the field and collaborate.

Dr. Steele noted the high volume of studies done on Gulf War veterans that have been used to inform the 2008 report and the recent 2013 report. Those have come from three main sources, the studies on Gulf War veterans, studies done on animal models with low-dose chronic exposures, and studies on other populations exposed to things similar to GW veterans. The most research was done on psychological stress; data shows no connection between stressors in theater and GWI. The highest data driven evidence comes from exposure to PB and pesticides. Other data in exposure to oil well fires, nerve agents, and other exposures. There is very little evidence supporting the anthrax vaccine or depleted uranium. Dr. White added that the one of the strongest points is that no matter what the comparison group, the rate of this illness is 25-32% greater in every study. Something is going on here.

Secretary McDonald stated that he does not want a group of individuals who provide him with a single point of view. He thinks it is important to continue to change the Committee, so that everyone can be heard over time, rather than a singular voice. He believes that innovation is incredibly important. Dr. Steele agreed with his words, and noted that the group gathered at the meeting is extremely diverse.

Chairman Binns noted that what Secretary McDonald proposed to do was previously tried after the 2010 IOM report's release With VA's support, Dr. Maximilian Buja brought together individuals from different backgrounds – VA staff, this Committee, and VA's national research advisory committee. These groups broke the problem out into eight areas, and produced a very comprehensive draft strategic plan. The outcome was that when the groups got together to discuss the plan, the meeting was very positive. Almost immediately following these meetings, however, there were efforts to turn back the clock on their work. Chairman Binns asked that Secretary McDonald try to distinguish between individuals who are interested in furthering the area, and those who are trying to push back against progress in understanding Gulf War illness.

Secretary McDonald thanked everyone for their efforts, and he looks forward to hearing from everyone at the Committee meetings moving forward. It is important to find the truth, and to rally around it.

The efficacy of flupirtine in an animal model of Gulf War Illness
Dr. Mohamed Abou-Donia, Duke University

Dr. Mohamed Abou-Donia gave his presentation titled "Flupirtine protects against permethrin/ N,N-diethyl-m-toluamide (DEET)-induced brain injury in a rat model for Gulf War illnesses". For presentation slides, please refer to **Appendix A – Presentation 6.** He began his presentation with a brief overview of Gulf War illness, including symptoms and the environmental exposures that Gulf War veterans were exposed to. Flupirtine is an analgesic drug that acts as an antagonist of N-Methyl-D-aspartate (NMDA) receptors. It is an anti-oxidant, and it protects against prion-induced neuronal cell death. Taking flupirtine in an oral daily dose can have beneficial effects on memory and sensorimotor deficits and headache/migraine and abdominal spasms. Flupirtine also does not induce development of dependence or tolerance, and does not have prominent side effects.

Dr. Abou-Donia posed the hypothesis for his study that flupirtine, helpful in the treatment of memory deficits and muscular disease in other patients, could potentially treat Gulf War veterans, whose major complaints include memory impairment and sensorimotor deficits. Specific aims of the study were to test the ability of flupirtine to protect from the

Gulf War Illness in a rat-model. Dr. Abou-Donia's previously developed rat model for GWI was used in this study. Four groups of rats were divided and treated as follows: control-daily for 60 days, DEET/permethrin-daily for 60 days, flupirtine-daily for 60 days, DEET/permethrin + flupirtine-daily for 60 days. Animals were evaluated for neurological deficits by determining clinical signs, sensorimotor functions, learning and cognition function, and pathological alterations. One day after the 60-day treatment period, the rats were evaluated for neurobehavioral and pathological parameters: rats from each group were evaluated for spatial memory by using the Morris Water Maze test and the other rats from each group were tested for sensorimotor performance. Neuropathological alterations were also carried out.

After testing and evaluation, results showed no statistical difference observed in the weights of animals treated within any group. The clinical condition of animals treated daily with DEET and permethrin or any combination of these pesticides and flupirtine was not different from that of the vehicle control or flupirtine groups. Spatial learning and memory were assessed using the Morris Water Maze (MWM). Results of the MWM showed that the vehicle and flupirtine had no effect, but that the DEET/permethrin treatment caused memory deficits, and that the flupirtine improved memory deficits induced by the DEET/permethrin treatment. Sensorimotor performance was assessed by behavioral tests including beam walk and score, incline plane performance, and forepaw grip time. With the beam walking and beam score, animals treated with DEET/permethrin showed significant deficit in beam walk score and time, compared to the vehicle control and flupirtine. Flupirtine reversed the effects of DEET and permethrin. With incline plane performance, animals treated with DEET/permethrin exhibited significant impairment in incline plane testing compared to vehicle control and flupirtine; flupirtine reversed the effects of DEET/permethrin. For grip time, animals treated with DEET/permethrin caused impairment in forepaw grip strength testing compared to vehicle control and flupirtine. Flupirtine reversed the effects of DEET/permethrin.

Hematoxylin Eosin (H&E), a staining method revealed neuronal degeneration in rats treated with DEET + permethrin in comparison to the three other groups. These degenerated neurons were characterized by dark eosinophilic staining of both cell body and proximal dendrites. The most obvious neurodegeneration was present in the motor cerebral cortex, the hippocampus, and the Purkinje cell layer of the cerebellum. Brains from the DEET/permethrin and flupirtine treated animals showed occasional dying neurons in some animals; the overall cytoarchitecture remained comparable to that of animals from vehicle control of flupirtine groups. In the cerebral cortex, H&E revealed degeneration in both the superficial and deeper regions of the motor cortex. The majority of degenerating neurons were of the pyramidal type. Flupirtine greatly reduced the number of dead neurons. Brains from animals treated with DEET and permethrin

exhibited neuronal degeneration in the dentate gyrus and the Cornu Amonis (CA) CA1 and CA3 subfield of the hippocampal formation. Flupirtine again greatly reduced the number of dead neurons. In the cerebellum, DEET/permethrin increased the numbers of dead cells in the Purkinje layer and the granular layer. In the cortex, immunostaining the DEET/permethrin treated animals with glial fibrillary acidic protein (GFAP) demonstrated hypertrophy of astrocytes with increased GFAP expression. Flupirtine greatly reduced the reactive GFAP. With regards to hippocampus, immunostaining with the DEET/permethrin treated animals demonstrated hypertrophy of astrocytes with increased GFAP expression in the molecular layer and the CA3 subfield of the hippocampus. The DEET/permethrin + flupirtine treated animals did not show any damaged cells.

The results suggest that flupirtine could potentially be used as a safe prophylaxis to protect from chemical-induced nervous system injury. Results also suggest that flupirtine may be useful in treating veterans with mild or moderate symptoms resulting in improvement of patients' quality of life. Moving forward, other scenarios with varying periods of exposure to DEET/permethrin and treatment with flupirtine should be tried to find the optimum condition for successful treatment with flupirtine.

Dr. Abou-Donia then asked for any questions after concluding his presentation. Dr. Sullivan thanked him for the presentation, and noted the highly collaborative effort of this study. Dr. Abou-Donia hoped that the staining model will help to better inform antibodies as well as objective markers, and will help to encourage larger studies. Dr. Abou-Donia noted that the collaborative efforts were considerable, and hopefully they will continue moving forward.

He then briefly discussed the autoantibody pilot study that he had recently conducted in collaboration with Boston GWI researchers. His research had compared autoantibodies as specific biomarkers for GWI. He hypothesized that the hallmark injury in GWI is in the brain and central nervous system (CNS). He then discussed that he had determined a pattern of autoantibodies that were activated by the injury caused to the brain in veterans with GWI. Literature has shown that this is not an entirely unique idea. Other studies use these proteins that leak from the brain into the blood through the blood-brain barrier to correlate with stroke, traumatic brain injury and other brain injuries including those chemically induced. The proteins, however, are very short lived. The autoantibodies to these proteins continue to be active for a long time afterwards, which makes them ideal to examine. In the pilot study specifically, Dr. Abou-Donia and colleagues looked at twenty samples of veterans with GWI, and ten controls. The autoantibodies for brain proteins that were analyzed indicated markers for demyelination, acute brain injury, and axonal degeneration in the GW veteran samples. Dr. Abou-Donia will look to publish the

preliminary results as a case series study because of the small size of the pilot study sample. This pilot study showed a distinct pattern in proteins and autoantibodies in GW veterans with GWI compared with the control group, which could form the basis for a testable blood biomarker, but a larger study is necessary to prove a statistical difference between groups. He noted that even though numbers were small comparing control versus sample group, the differences were distinct. The results need to be examined in a larger study, moving forward to validate these promising initial biomarkers results in veterans with GWI.

Dr. O'Callaghan asked if Dr. Abou-Donia had seen other neurotoxicants where they were able to retrieve breakdown products that were exposed to the immune system. He sees issues where signals do not go on for long enough to be seen. Could it potentially be ramped up sensitivity-wise so that everything there could be seen. Dr. Abou-Donia said that this was something he planned to look into. Dr. Steele asked with regards to the antibodies, whether there were other neuronal proteins seen. Dr. Abou-Donia noted that other proteins were seen, but the others were there. He hopes to be able to identify these proteins to understand each of the disease signatures. Chairman Binns asked if any of the preliminary research suggests any specific treatment targets. Dr. Abou-Donia said that this does. There is no doubt that there is one scheme that can show in a mechanistic way how this illness works. Hopefully when the bigger picture is seen, they can understand exactly what it says. Dr. Crawford asked whether this is disease specific or could apply to other neuronal diseases. Dr. Abou-Donia noted that they were not sure at this point, but it was his hope that with continued research they would be able to say that this was the signature of Gulf War illness.

Chairman Binns noted the significance of this presentation and the collaborative effort put forth by many members of the Committee.

Public Comment

Chairman Binns asked that those who would like to speak for public comment to do so.

Mr. Ronald Brown spoke for public comment. He addressed the presumptive conditions that need to be granted to Gulf War veterans. He was told that VA would not act on legislation for the presumptions because of the cost. He reminded them that cost was not an issue when they went to war. Remarks regarding cost are offensive; people are dying because they don't receive the benefits they have earned. He would like to see elected officials put the veterans first. He thanked Committee members, especially those who would no longer be a part of the Committee following the meeting. The VA has faced many challenges where improvement is needed. The first goal would be to regain the trust of the veterans. If the VA is not willing to help fix these errors, this would not be

acceptable. It is necessary to implement treatments and protocols, because without this implementation, veterans will not get the help they need. The ORD has done a great service to research, they need to do Gulf War research. Pilot studies that have shown promise need to be conducted on a larger scale. GWI is still around, despite the time that has passed since the Gulf War. Veterans are dying from cancers that do not have presumptions. He stated that the National Gulf War Resource Center (NGWRC) was present to be a voice for those families of the suffering. He was told at a recent meeting with the VA that they were working as hard as they could. He does not feel comfortable telling this to the families of deceased or dying loved ones. He thanked everyone for the opportunity to speak.

Maj Denise Nichols spoke next. She wanted to remind everyone that the Committee was about research on Gulf War illness. She would like to see live web streams of the meeting, so that veterans who cannot be present can see the meetings, for not only veterans, but for other doctors and researchers so that they can be informed. The meetings should be publicized, and that could open up a number of opportunities for research. She noted the lack of respect for the people that did make the trip to the Committee meeting. Being told that they were not allowed to comment during the meeting was not appropriate. The VA was present because of the veterans. The questions being asked were in line with discussion. Maj Nichols pointed out that this attitude does not help the situation. She thanked everyone for their time.

Anthony Hardie spoke for public comment. A member of Veterans for Common Sense, Mr. Hardie spoke of the consumer reviewers used by the CDMRP Gulf War Illness research program. Veterans interested in that role should express their interest. He would like to see fair participation in research programs. With regards to Dr. Dursa's presentation, he noted his concern on the lack of conditions asked about, and that they are referred to as CMI, and not GWI. They should be using the two main definitions detailed by the IOM and by Dr. Steele. The survey should be re-conducted every five years, until every veteran has passed. The studies presented also failed to account for 75,000 veterans. The cutoff date being used for GW deployment was the reason, and he thought this was troubling. Individuals present after the cutoff date were still exposed to the same exposures so were not really 'controls'. The same was true for Gulf War Era Veterans. He also noted the significance of those individuals who could not be asked if they had brain cancer, because they had already died of it. Anthony Hardie thinks and hopes that the Secretary's presence signifies a reset button at the VA. His appearance at the meeting was very promising. He thanked everyone for the chance to speak, and the Committee for their time and effort to try and help the veterans.

Margaret Dunn spoke for public comment; she was a Gulf War nurse. She wanted to talk about the expansion of research from the fields currently being pursued, such as seizures or migraine headaches. It was important to make sure they look at those overlooked issues. She discussed the education of doctors at the VA. She recently attended her hometown VA meetings. The two chiefs of staff at the meetings agreed that the VA dropped the ball with Gulf War veterans. Doctors were not educated and make false diagnoses. There was a huge communication problem at the VA medical centers. Information was not being disseminated to physicians, and benefits were not being provided to them. She added that ICD codes for toxic neuropathies, toxic effects of organophosphates were not being used. . She asked why these codes were not being used, when proof of exposure to these things exist. She thanked everyone for their time.

Glenn Stewart spoke for public comment. He wanted to elaborate on the Ms. Dunn's comments on the physicians failing to diagnose their illness. He has fought with the VA since 2010. His last exam at the WRIISC center showed that he had Gulf War illness, listing out all of his symptoms. He brought his results and a number of supporting documents to his appointment at the VA medical center. His claims were denied completely. The physician who examined him agreed with the conclusions drawn by the WRIISC. People are involved trying to fight the rejection, the claims were done wrong. He was told he would have to go through an appeals process after the claim was closed out. The physicians performing the evaluations need some real training, bottom line.

Neil Brucker spoke next, a Gulf War veteran. He asked that the researchers add funds for housing, transportation, and food so that they can be a part of the research studies proposed. He stated that some of the treatments currently funded may not directly be GW related and are not even allowing Gulf War veterans under VA care to participate in these treatments. They should be made available to Gulf War veterans. He has contacted a number of people trying to get these treatments, and has faced denials. Veterans should be able to tap into these resources, when treatment options are out there.

Ed Bryan spoke next. He had a few questions for the Committee. What is the death rate for Gulf War veterans? The presumption list needs to be updated, why had this been idle for so long? There needs to be a good definition between GWI and CMI. Physicians need to know how to treat veterans. The treatment list needs to go from research to clinics. Money needs to be allocated for research into treatments. He asked for more physicians with exposure expertise. He appreciates the work of the Committee, and has high hopes for the new Secretary.

John Montecarlo spoke next. He asked for his fellow veterans to get out whenever they could, just to get some fresh air and a little exercise, this could help a lot of people. He

has found it very beneficial personally. The massage machine has helped significantly when in pain at night in bed. He also noted the help of his chiropractor. There are people out there looking to help. He really enjoyed hearing all of the people talk. He thanked everyone for their time.

Dean McGovern Jr. spoke for public comment. He thanked all of the veterans for their testimony. He spoke of the need for compensation, for treatment, for the benefits they deserve. He has been treated time and time again, but the VA claims do not compensate on those diagnosed illnesses. He suffers from sleep deprivation, and was not allowed a sleep apnea machine. He was told that he was not eligible or entitled for treatments he and the rest of the veterans deserve. He thinks that education goes a long way, and thanked the Committee for the chance to speak.

Peter Greene spoke. He thanked Chairman Binns for his service on the Committee. He hopes that he will continue to stay active in the Committee. He noted that educating physicians on Gulf War illness is incredibly important.

Chairman Binns concluded the first day's meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses. He commended the VA senior staff for remaining present during the entire meeting, and for taking detailed notes on the issues. The meeting was adjourned.

DAY 2

Chairman Binns called to order day 2 of the meeting of the Research Advisory Committee on Gulf War Veterans Illnesses. He made note of the change in facilities to the meeting location in Crystal City, VA. He wanted to begin with a response to Secretary McDonald's visit to the Committee meeting on Day 1. There was a VA press release from the previous night that echoes statements made before, which were misleading. The press release said that VA was paying benefits to hundreds of thousands of Gulf War veterans, but failed to state that VA considered the Gulf War "era" to still be continuing. So almost all of these veterans receiving benefits had served in the recent wars in Afghanistan and Iraq, not the 1991 Gulf War. Chairman Binns asked for Mr. Bunker to send him the benefits data that he had mentioned to Chairman Binns the day before.

Chairman Binns had drafted a letter, thanking Secretary McDonald for his attendance and continued efforts on behalf of GW veterans. He shared copies of the draft letter with the other members. Chairman Binns said that those Committee members who would like to sign and submit the letter were welcome to do so before he sends it along to the Secretary.

Dr. Klimas asked whether it was true that the previous training modules trained physicians to consider GWI to be a psychosomatic problem. Dr. Golomb noted that the training had a dismissive attitude that conveyed the impression that this was not really a valid illness. The general feeling was one that led to the attitude that physicians are dismissive towards GW veterans. Chairman Binns reworded the letter to reflect that physicians were "not trained to consider it a serious illness".

Dr. Klimas asked for a use of consistency in using Gulf War illness as the language over chronic multisymptom illness. She thinks that a summary letter from the Committee might focus on research priorities and clinical care, rather than focusing on the past missteps of the VA. Consider instead as a letter detailing priorities moving forward. Chairman Binns encouraged Committee members to prepare such a recommendation in addition to this letter from the Committee, to also write to Sec McDonald individually. But he pointed out that this letter was not addressing past problems, but those the Committee had witnessed just the day before. Mr. Bunker noted that it was important to remember that in the survey, some of those nondeployed veterans were deployed to theater after the cutoff date.

Dr. Klimas clarified some of the language, with the need to get things in context with regard to recent comment dates (as in the day prior). Chairman Binns confirmed these changes, and clarified wording on deployment dates to reflect Mr. Bunker's comment. The draft letter having been agreed upon by all members present, it will be sent to the Secretary as a formal recommendation.

'How to discussion': GWI exposure assessment and biomarker development
Dr. Kimberly Sullivan, Associate Scientific Director

Dr. Kimberly Sullivan began the 'How to discussion' on Environmental exposure assessment and biomarker development. For presentation slides, please refer to **Appendix A – Presentation 7.** She provided a brief overview of how pesticides were used in the Gulf War theater. Troops used pesticides for personal use on skin and uniforms, and as insect repellants, area sprays/fogs, pest strips/fly baits, and as delousing agents for prisoners of war (POWs). During the 1990s, the military used one million pounds of pesticides per year. The field guide for maximum protection included permethrin on the uniform and DEET on the skin as a properly worn uniform. Pesticides were used widely in the GW to protect troops. These pesticides were used in areas where troops worked, slept, and ate. A Health Risk Assessment conducted by DOD estimated that 43,000 GW veterans could have been overexposed to these pesticides, and this number is likely an underestimate because it does not include mixed exposures. Other relevant environmental exposures Gulf War veterans may have been exposed to include

anti-nerve gas pills, pyridostigmine bromide (PB), and sarin/cyclosarin at the Khamisiyah weapons depot detonations.

Gulf War exposures have been measured using self-report surveys, wind pattern and exposure modeling, and blood biomarkers for downstream effects. Self-reported environmental exposure surveys available to all researchers interested in using them include the Kansas Environmental Exposure Survey and the Structured Neurotoxicant Exposure Checklist (SNAC). The Kansas Environmental Exposure Survey assesses exposures including PB, pesticides, depleted uranium (DU), and oil well fires. The SNAC assesses occupational exposures including military, non-military and hobby-related exposures. Dose exposure models developed by DOD include the sarin/cyclosarin dose-exposure modeling and the oil well fire dose modeling. These models are available through the DOD. The Committee detailed in the 2014 RAC report recommendations for improved methodology guidelines for epidemiological research, including a number of analyses and modeling techniques. With regards to biomarkers in Gulf War illness, there exist no laboratory tests that accurately diagnose individual patients with Gulf War illness, but studies have identified objective biological measures that distinguish between groups of ill GW veterans and controls.

The path to biomarker development, as summarized by the FDA, includes biomarker discovery, qualification, and application. Dr. Sullivan detailed the guidelines suggested within each development section. She used the neurological/neuropsychological health outcomes research as an example that has found significant findings in biomarker development between exposed groups. The Chao et al 2010 and 2011 papers studied the sarin and cyclosarin exposures through MRI scanning and neuropsychological testing. Health outcomes in each of these studies found significantly reduced gray matter, hippocampal volumes, and total gray and white matter volume in exposed veteran groups. Toomey et al (2009) examined PB, pesticides, vaccines, immune globulin (IG) injections, and oil well fire smoke and neuropsychological testing outcomes. Results showed that deployed Gulf War veterans had significantly lower scores on tests of verbal memory, verbal learning, motor speed, and attention. The Committee recommended that given the consistency of findings relating GWI to neurotoxic exposures that high priority be given to studies that further characterize specific effects of Gulf War related neurotoxicant exposures. The IOM recommended that biomarker research areas should include: inherited genetic variants, molecular profiles of gene expression, other epigenetic markers, specific viral exposures, signature of immune activation, and brain changes detected through imaging.

Dr. Sullivan discussed the Committee recommendations on exposure assessment and biomarker development, which can be found in the attached presentation and the 2014 RAC Report.

Dr. Nancy Klimas, Committee Member

Dr. Nancy Klimas delivered her presentation specifically on Biologic biomarkers in GWI. She provided a brief overview of the biomarker purpose, noting that GWI biomarkers might be found through neuroimaging, clinical objective measures, and laboratory based markers. Neuroimaging includes MRIs for anatomic differences, white and grey matter decreases, and localized areas with abnormal findings. The clinical objective markers include physical evaluation (PE) findings, and objective markers of cognitive function. Laboratory studies of biomarkers in GWI include blood studies (the most common), and attention to a specific compartment, such as blood, spinal fluid, and the gastrointestinal tract.

Dr. Klimas then discussed the identification of biomarkers with therapeutic implications. It is important to have mapped mechanisms of the illness to identify the most effective intervention points. Myalgic encephalomyelitis (ME)/Chronic Fatigue Syndrome (CFS) and Gulf War illness are both complex disorders with an overlapping number of symptoms, which affect several of the major regulatory systems. A comprehensive survey of endocrine-immune function should be conducted: gene, cell and immune protein levels. Dr. Klimas showed a table with the effects of exercise on biomarkers, given the Friedman test results and the reaction the biomarkers had. With exercise, cytokines showed significant changes across a broad range of the markers. With regards to immune activity, chronic immune cell activation and dysfunction have been found. Recent research showed that NK cell function in GWI was more responsive to Interleukin-15 (IL-15) than in chronic fatigue syndrome. Treatment with the IL-15 reduced the topological distance between GWI and normal health individuals by over 30%. Dr. Klimas noted that these data were still in preliminary stages.

Dr. Klimas moved to the study on the therapeutic roadmap of ME/CFS: dynamics of mRNA and miRNA profiles in relapse lead to treatment. The rational being that ongoing work showed broad changes in metabolic pathway activation, and that miRNA was a key transcriptional regulator of these pathways. Infectious disease in GWI was not a recent focus of research, but new tools brought infectious disease back to the table. This was because with GWI, in a system with demonstrable poor cytotoxic function, consideration of co-morbid infection should be considered. The role of pathogenesis was discussed. Infection could play a role in GWI in a number of ways: by triggering infections inducing downstream events, persistent infections, recurrent infections, reactivation of latent infections, and microbiome shifts and molecular mimicry inducing autoimmunity.

In triggering infections inducing downstream events, infections endemic to the Middle East included Q fever, hepatitis, malaria, brucellosis, and a number of others. The risk in theater triggering these infections include leishmaniasis through the sand flea vector, water borne illness, airborne illness, and germ warfare. Dr. Klimas discussed gastroenteritis and irritable bowel syndrome (IBS). Compared IBS rates before deployment to during, and after deployment eighteen years later were 5.8%, 38.9%, and 33.6% respectively. Deployed veterans who were exposed to an infectious gastroenteritis are at greater risk to be later diagnosed with IBS.

Persistent infections include bacteria such as mycoplasma, chlamydia, and Q fever. Amoeba, parasites, malaria, fungal diseases, viral acute infections, and novel infections are also persistent. New methodologies that identified pathogens by sequence data or multiple probes could improve the understanding of persistent infections. The reactivation of latent infections was covered following recurrent infections. Immunomodulatory function may contribute to the pathophysiology of diseases caused by these viruses. The last way described where infection might play a role in GWI was – microbiome shifts and molecular mimicry inducing autoimmunity. The role the microbiome plays in health is an emerging field. The gut contains microorganisms that share a structural similarity with neuropeptides involved in regulating behavior, mood, and emotion. This is called molecular mimicry. The microbiome has been shown in studies to induce neuroinflammatory states. A single course of antibiotics can significantly alter the microbiome with only partial recovery up to four years after treatment. There are a number of future directions to take with biomarkers. New methods allow research to relook at past ideas with more powerful tools. Whole genome sequencing is a powerful tool. Comprehensive clinical assessments and utilizing computational biology approaches to handle big data can be combined with neuroimaging tools. The field can use said tools to answer complex questions faced.

Dr. Baldwin and COL Chagaris were given the opportunity to speak after Dr. Klimas' presentation, regarding Q fever. Dr. Baldwin is a molecular biologist at the applied technology and genomics center at the Wright-Patterson Air force Base. COL Chagaris served in Iraq in the mid-2000's and became ill with an undiagnosed condition, which he ultimately deduced to be a form of Q fever. After asking physicians to treat him for Q fever, he recovered and subsequently authored a paper on his experience and reasoning.

COL Chagaris discussed the need to figure out where to find and follow through on credible hypotheses of complex illnesses. His hypothesis suggests that Q fever in conjunction with PB and pesticide exposure allow for the development of a unique form of Q fever. He hypothesized that infection is perpetuated, and thus a chronic illness is formed. When the article was written, there was no way to test for the specific bacteria

pertaining to the Q fever. The bacteria was only recently able to be grown in the lab, there is still a lot to be done to further develop diagnostic tests.

He turned the conversation over to Dr. Baldwin, who would discuss how they might be able to begin to test for these kinds of bacteria or illnesses. He stated that there was a need for a treating physician to be given a list of possible organisms, which can be matched to symptoms experienced by the patient. When this map would be put together, the patient will have the most potential to be effectively treated. There exist potential for bio warfare or some other new problem. Being able to anticipate these new and overlapping exposures is necessary. Organisms change over the course of treatment; isolating a bacteria or organism at the point of contact may be out of date if and when the organism changes outside or beneath that site and point.

There is a possibility that in five years the ability to sequence on location will exist. The entire gene expression of blood can be sequenced. It may not be the organisms a person has, but it is the genes that those organisms express, that are most important. Being able to see the infection leads to the opportunity to provide therapeutic intervention. Sequencing allows at the very least to know if there is something before unseen, for scientists to cross off of the list a number of things to better hone in on the possibilities. Preliminary information observed on respiratory infections, for example, was found to have bacterial roots. Many individuals had not seen this before. Many pathogens live within people who are asymptomatic, and may activate if a person is immunocompromised or under stress. At his center, they look at technologies, including sequencing and genomics, to try and use this technology to best help physicians to treat patients.

Dr. Klimas noted the importance of looking at the big picture in patients and subjects, not just narrowing focus on specific areas or thoughts. Looking at the big picture allows for things to be seen that before would not have been. Changing the microbiome for therapeutic benefit is a new intervention and is one benefit of acting in this way.

Chairman Binns asked if specifically using these technologies today, one may be able to detect a latent Q fever syndrome or other illnesses. Dr. Baldwin noted that this was in fact possible. It can be restricted to time space in RNA of what is going on in the present. The answer would be yes, but if the virus is long-standing in the individual, the chances of picking up on it may go down. Dr. Klimas noted it was important to consider whether they had the materials needed to be able to properly explore the proper components. In terms of whether they are missing Q fevers, it is important to consider whether the toxic environment these individuals were exposed that have evaded diagnostic capability. The ability for physicians to have a tool created for pathogen discovery that allowed for them

to look for a lot of species in a physician that would be immensely helpful. She thinks that science is close to this. Chairman Binns noted the similar studies going on at Columbia University. Dr. Klimas noted that this was the case. They were in the process of collecting samples to test. Methods were not perfect, the field is quickly growing, and it is important to get Gulf War veterans into this platform of discovery.

Dr. Sullivan thanked Dr. Klimas for talking about biomarkers, and thanked Dr. Baldwin and COL Chagaris for discussing their work. She wanted to take a moment to talk about the consortium study that works to put all of these pieces together. They are trying to identify CNS biomarkers, blood measures, spinal fluid, and susceptibility markers. With exposure based illness, it is curious why some people get ill and others don't. The model for the consortium builds all of these pieces, and it is important to try and put all of these markers together and see the big picture.

Dr. Agarwal thanked Dr. Baldwin and COL Chagaris for their work, and is very interested in seeing what happens moving forward. Dr. Baldwin noted that certain microorganisms produce toxins that have neurotoxic events, that some of these veterans have experienced symptoms of. Chairman Binns asked whether in a research study, if GW veterans blood samples could be sequenced, a list could be developed of the different organisms, diseases and illnesses they have. Dr. Baldwin said that this was possible, at the current time the test would be expensive and slow, and $2000 to $3000 per sample to run. Dr. Klimas asked for Dr. Baldwin to clarify on the subtraction idea. Dr. Baldwin said if all DNA was sequenced from a sample, it will produce a lot. If they reverse map this against the human genome, they can identify those non-human organisms. What is left are the genes of the organisms in the sample that are not human in nature. He is not sure of the specificity or sensitivity on a human sample to date, because human tissue sampling was limited at that point. They do not need the entire genome of the virus or bacteria in order to make a very accurate diagnosis. All that is needed is a non-trivial area of the genome.

Chairman Binns thanked everyone for their presentations, and noted that this was a potentially promising new direction for Gulf War research.

Recognition of retired/retiring Committee members
Dr. Roberta White, Scientific Director

Chairman Binns brought the program to order for the recognition segment of retiring/retired Committee members.

Dr. Roberta White thanked everyone for being present for this section of the meeting, as the Committee would be honoring the retired/retiring Committee members. For

presentation slides, please refer to **Appendix A – Presentation 8. Chairman Binns presented first on** Steve Robinson.

Chairman Binns noted Steve Robinson's recent passing. He was an original member of the Committee. Much of his military career was spent in the field. Chairman Binns thought he would know a lot of the people at his memorial service, but he discovered he only knew about 10% of the people present. This was because Steve Robinson had affected so many people over the course of his career and life. When Mr. Robinson joined the Committee, he was very angry because of the government trying to cover up GWI. Within five years, he was incredibly polished, mature, capable, and reasonable spokesperson for Gulf War veterans. Chairman Binns is very proud to have known him.

Dr. White noted that this was the most significant change in members since her tenure on the Committee. The Committee has gone through a number of changes, including changes in structure and the charter, but the dedication shown by these members was exemplary. They have contributed substantially to the RAC and to the VA in their efforts. She spoke of the following individuals: Anthony Hardie, RAC member from 2006-2014, LTC Marguerite Knox RAC member from 2002-2013, William Meggs, MC, PhD RAC member from 2002-2013, Reverend Joel Graves, DMin (Army Captain, retired), RAC member from 2002-2014, James O'Callaghan, PhD, RAC member from 2005-2014, Lea Steele, PhD, RAC member from 2002-2014, and the Scientific Director of the Committee from 2003-2008, Chairman Jim Binns, Chairman of the Committee from 2002-2014. Dr. White provided a brief biography of each member, and noted their accomplishments and activities while a part of the RAC Committee. An exact record of the comments can be found in **Appendix B.**

Dr. Bill Meggs

Dr. Meggs said that it has been a great honor and privilege to have been able to serve on the Committee. He has developed tremendous respect for the Committee members. The contributions he has seen members of the Committee make have been amazing. He applauded the efforts that veterans have made to be present, and noted the hard work they have successfully put into staying up to date and fluent in the research. He thanked everyone for the opportunity to work with and among them, and is very proud of having been able to be a part of the Committee.

Dr. Jim O'Callaghan

Dr. O'Callaghan said that it has been a privilege to serve as a member of the Committee. The Committee has affected him in many ways. His lab is now primarily focused toward Gulf War research. He looks forward to continuing Gulf War research and to serving the Committee and this field in as many ways as he can.

Dr. Lea Steele

Dr. Steele thanked everyone for the chance to have been on the Committee. She thanked Chairman Binns for the opportunity to jump on this Gulf War enterprise. She is proud of the work the Committee has done, and truly believes that the Committee has made tremendous headway in understanding this illness.

Recognition of Chairman Binns

Dr. Steele made a few comments on Chairman Binns' tenure on the Committee. Everyone came to the early meetings hoping that the science would tease out all of the challenges. She marveled from the beginning at Chairman Binns' diplomacy. He was the perfect person to direct the Committee. He was insightful, well informed, persistent, and this has remained the case over the years. She does not think there would be a Gulf War research enterprise if not for Chairman Binns. He has been legendary for his persistence, but also for his wisdom and ability to see things all the way through.

Chairman Jim Binns

Chairman Binns thanked everyone for their kind words. He has been doing this for almost thirteen years, and was as surprised as anyone that this much time had been dedicated to GWI in the course of his life. He noted that he has been fortunate to be able to do some very interesting things in his career. This has been the most frustrating but also in some ways the most rewarding project he has worked on.

This job never left him wondering what he was going to do from day to day. It was a tremendous learning experience for him, in how Washington DC and the government operates. The exceptional colleagues he has worked with made this an exceptional experience. The wide range of backgrounds represented in the people he has worked with has been remarkable. Some of the top scientists of this generation have been a part of the Committee and have worked with the Committee. It has been a female-run outfit at the research level, and the Committee is better for it.

The veterans he has gotten to know have also been from a wide range of backgrounds. The officers who have been involved were lieutenants, captains, and majors. Many enlisted men and women have been the leaders of their fellow veterans. Steve Robinson was a prime example. He became the best spokesperson for GW veterans that ever existed. The veterans still present, who have not given up when it would have been easier to do so, should be commended. It was a privilege for Chairman Binns to get to know

every one of the veterans. This illness does not discriminate; it affects all people at all levels.

This Committee has made a difference, and no one in the room can argue that. There has been considerable scientific progress made. He believes this progress is accelerating at this point. He thinks that this problem is on its way to be solved, to having results produced. The IOM Report in 2010 gave the Committee, researchers, and VA the assurance that treatments could still likely be found, that Gulf War Illness research was still worth investing time and funding in. This gave Chairman Binns another wind in his efforts. He discussed the consortiums, noting the importance of these. Getting everyone together to work on the problem was so much more efficient and likely to produce results than the typical siloed funding model typically used. He firmly believes that Gulf War illness will be solved, and it will be solved by the people in this room. He thanked everyone for their huge contributions; he knows that many of the people in the room have made this their life work. This effort has been a prime example of the aphorism that a small number of people that want to make a difference can do so. Chairman Binns stated that he will continue in some fashion to be involved in Gulf War Illness research.

Dr. Golomb reiterated the comments of Dr. White and Dr. Steele. She thanked Chairman Binns for all of his hard work. She does not think Gulf War illness would be anywhere close to where it is today if not for his efforts. The Committee will feel an incredible loss from the members that it will be losing.

MAJ Denise Nichols made a comment on behalf of the veterans. She commended Marguerite Knox's efforts; they were fellow nurses during the war. MAJ Nichols saw her continue to fight, and the veterans stood behind her. Chairman Binns goes to the heart of the matter, that no veteran leaves another veteran behind. The veterans knew Chairman Binns was a fellow brother in their fight. They saw his expertise, and how he led them through Congress, and testified on their behalf. Chairman Binns was a great diplomat. Veterans outside of the United States have felt left out because they have had no champion in their countries like this Committee.

She remembers Steve Robinson. She met him, and she knew he wanted to help. He stood up for veterans, traveled all over the place. When people were not getting treated, he was down there trying to put a stop to the unfair treatment of veterans. Joel Graves was not big in the veteran community before being on the Committee. He brought a quiet confidence to the Committee and became a very elegant spokesperson. Anthony Hardie has done so much. It was an honor sitting next to him during testimonies for Gulf War veterans. Dr. O'Callaghan's testimony was hugely impactful. She does not know how they will do without each of these members that are leaving. MAJ Nichols met Dr. Steele

in April of 1994. She knows that no one will walk away from Gulf War veterans or Gulf War illness. They appreciate the efforts put forward by all of the Committee members. The Committee has not let the veterans down, they have continued the efforts. She thanked them sincerely for standing by them all of these years.

Dr. Sullivan said that it has been an absolute pleasure working with Chairman Binns. She learned a lot from him on how to never give up. His persistence and perseverance has kept the Committee going, and she really appreciates all of the work that he has done. The same holds true for every member coming off of the Committee. Her only consolation will be that she will continue to get to work with most of the retiring Committee members in other research capacities.

'How to discussion': GWI study recruitment
Dr. Beatrice Golomb, Committee Member

Dr. Beatrice Golomb presented a 'How to discussion' on Gulf War illnesses study recruitment. She provided a brief overview of the recruitment approach. For presentation slides, please refer to **Appendix A – Presentation 9**. It was important to recognize that recruitment will not be a passive approach; it is the largest failure point for clinical trials. The plan moving forward is to devote considerable effort in this direction. Studies fail not only because of a lack of resources devoted to the study, but also because risks imposed on participants have ceased to be balanced by potential benefits. Studies often underestimate recruitment challenges, extend recruitment periods, or incur higher than anticipated study costs to achieve recruitment targets. As a result of these issues, there has been a call for researchers to report recruitment strategies and costs for the benefit of other researchers.

Dr. Golomb began to discuss her recruitment methods in her paper 'Recruiting a special sample with sparse resources: Lessons from a study of Gulf War veterans'. She said that is was beneficial to try multiple low cost approaches that each may provide low yield but together may succeed. She noted that the study her research refers to recruited veterans with Gulf War illness, and not healthy deployed or nondeployed controls. But since the paper's publication, they have successfully recruited those other participants as well. They used both nationally targeted and locally broad approaches for recruiting through the media. They used special interest groups like the United Veterans Council of San Diego and the Riverside County VA Veterans Services; emails and presentations to each of these groups. They used local physician outreach to recruit. They used the internet to recruit through study specific websites including the study splashpage website, a Facebook page, and a Myspace page. The Gulf War specific websites were also used including ngwrc.org, gulfweb.org, and gulfink.osd.mil. Referrals were utilized, by existing participants, friends of participants, friends of recruits, and from other studies.

Local free advertising in Craigslist and Backpage were also a source of recruitment. Backup approaches to consider would include the DOD Defense Manpower Data Center (DMDC) GW veteran listings. Dr. Golomb thanked everyone and asked for any questions.

Dr. Klimas noted that the local reserve unit was a great source for finding controls. She found that her frustrations at her inability to access and get GW registry information was discouraging. Dr. Steele has done some recent GW registry work. Different facilities have given investigators access and perhaps this could be a local VA issue. She reached out to Dr. Bossarte on how they can make this information more available to VA researchers across the country. They are very interested in helping with this and making it available to researchers. This effort has been started in the last month or so. A systematic access routine or protocol should be established. Dr. Klimas noted that it was important to ask and try to figure out how to spend less time, effort, and resources on finding individuals to recruit. Substantial chunks of budgets are spent on travel, because there is no locally organized group established to help find these regional individuals.

Dr. Sullivan noted that research studies will not be effective unless recruitment can get done. Dr. Golomb agreed with this, and thought that it was important for investigators trying to get studies off the ground to know how challenging recruitment is in a study. Dr. Ashford noted the WRIISC center's recent charge to ramp up recruitment efforts, and would really like to work with Dr. Golomb moving forward. Dr. Steele said that using the GW registry roster would be beneficial for a lot of reasons. They can be found based on region, but would also be a scientifically stronger sample of the population as well. It has been challenging to access the rosters. The development of a recruitment tool was being worked on, where people volunteer themselves into a new list that is protected but can assist investigators in their recruitment. Investigators want to recruit, veterans want to participate; it would be a matter of getting these people in touch. Dr. Sullivan noted that fostering existing cohorts was also important. It takes a lot of work to keep these groups of individuals enrolling. Dr. Golomb noted that it might be important to note that retaining these recruits is just as important as recruiting them to begin with. Shooting for the best recruits, those that are representative is important, but getting those that meet the criteria is an important aspect as well.

Chairman Binns noted that these criteria and sections will be pulled together and put into a manual to be displayed on the website. The more specific that members can be in these manuals, the better off everyone will be.

Mr. Bunker asked Dr. Golomb about the CoQ10 article, and whether they were looking to do a larger study submission. Dr. Golomb will be taking a slightly different direction

going forward with treatment development. Rather than expand the CoQ10 study, they will be looking for finding the best possible treatment as quickly as possible that will provide a greater benefit. She felt that CoQ10 is most optimal when paired with other treatments.

Chairman Binns will incorporate the changes in the letter to the Secretary and put the names in of those individuals who were at this meeting. He announced the public comment session.

Public Comment

Steve Hoehman spoke first. He thanked everyone for the opportunity to speak. He asked everyone to remember that everyone is present to help treat and possibly even cure Gulf War illness. Not knowing has caused more anxiety than knowing what is going on with veterans. They need to insure that treatment trials include travel, lodging, and meals for veterans when writing budgets into studies. He does have GWI as diagnosed by the WRIISC. He needs for information to be updated at the VA. He wondered why veterans are not on the new Gulf War veterans list. He asked how the VA was getting word out about WRIISC's to help with other research. He queried why the VA was not using social media for Gulf War illness outreach. He noted the efforts by MAJ Nichols and Anthony Hardie to keep veterans up to date on studies. He would like for the VA to take the members rotating off, and create a new Committee out of them to assist oncoming members. There should be a better distribution of information to VA medical centers from the information covered at the Committee meetings. He thought that the Gulf War registry should include an opt-in area where veterans give the okay to be contacted for research or studies. He was very pleased with the first day's meeting outcome. He was pleased to see that Secretary McDonald attended the meeting and was already knowledgeable about Gulf War illness. He thinks the ones who have the means to affect change for those than cannot, should. He thanked everyone for their tireless efforts for Gulf War veterans.

Denise Nichols spoke for public comment. She noted the first day's meeting, about the OPH results. She wondered why they don't look at equipment from the Gulf War. Those data from the prior day did not look the most accurate, because of the large populations of deployed and nondeployed veterans. Maybe a healthy civilian population should be used as a control. She is very enthused by the research being done. She feels like her fellow participants need to promote these studies to veterans who do not believe in the studies. She wondered what could be provided to individual veterans by the papers published on their individual health, because they often get nothing back, besides the paper published. She wanted to remind fellow veterans that this is not a blame game. They need to work together. The biomarker research seems very hopeful. She proposed a

large conference for idea generation of scientists and researchers. They can look at what was possible at the time. This could get a lot more participation. She noted the trouble she had with getting information on research. She asked for the VA to help get materials out to the public, to the veterans that need to see it. It could be hugely beneficial to get these out on bulletins at local VA medical centers. She thanked everyone for their time, and asked that the VA not think of veterans and the Committee at adversaries.

Dr. Klimas noted that in terms of individual data, they hold a patient conference every year in her clinic. This helps to give them an individual data set, and helps to get the information to them to promote inclusion and understanding. She believed that this helped with recruitment substantially.

Peter Sullivan of the Sargent Thomas Joseph Sullivan Center spoke next for public comment. He spoke with Dan Sullivan, his son. They were promoting improved health outcomes for current and former military personnel with complex health problems that were difficult to diagnose. They came to the Committee meeting to talk about their son and brother, who died from a similar health problem as a result of his time in Iraq. They thanked everyone for their efforts on the Committee. They were hoping that it will help people with GWI, and those that in the future serve the country and develop similar health issues. Mr. Sullivan was encouraged by the work he heard during the meeting. He is encouraged by Dr. Baldwin's work, and sees a lot of hope.

The work done here can absolutely apply to other wars that produce veterans suffering from an illness that is also very complex. Dan Sullivan was one of the cofounders of the Center. The Sullivan Center provides small grants for research specifically studying biomarkers. They also look to spread the word to the community and raise awareness. He told the story of his brother, and how he was treated for 'psychosomatic' illness, and then died shortly thereafter. Autopsy revealed significant problems internally. Illnesses like these are not psychosomatic in origin, but are as a result of military occupational exposures. Exposures are a key component in the diagnosis and treatment of Gulf War illness. Physicians at the VA need to be educated on this topic, and need to be able to in turn treat and educate patients living with Gulf War illness. A failure to apply basic principles of medical science to the veteran population would mean that these veterans are not being treated properly. He thanked everyone for the opportunity to talk, and looks forward to what is to come.

Angie McLamb spoke next for public comment. She wanted to note her appreciation of the dedication shown by the Committee. She got sick while deployed, and following her return home. She was troubled at the fact that no one had answers in the years following the Gulf War. MAJ Nichols told her about the Committee, and she wanted to tell them

that they are the voice of Gulf War veterans. She felt very alone before learning of the Committee. She plans to continue attending Committee meetings, and thanked everyone for helping veterans. She hopes that it will help treat veterans, but also future veterans, and possibly even the civilian community. Listening to the Committee was like a breath of fresh air. It was sad that Committee members were scheduled to leave, but she was happy to learn that a lot of people will still be involved in any way that they can. She thanked each of the departing Committee members. They have given ill veterans hope.

John Montecarlo spoke for public comment. He was working with chronic inflammation, and wondered whether anyone had information on how to help his symptoms. He noted MAJ Nichols comments on secondary exposure, and would like to see follow-up on that. He also wondered whether media were present for the meeting, and that they should be. He thanked everyone for their time and effort.

Dr. Klimas noted her talk about clinical management of Gulf War illness in the January 2014 meeting. She asked that he go back, take a look at that, and show it to his physician at the VA. The low-dose naltrexone trial that Dr. Meggs had spoken of the day before could also be beneficial.

Julie Mock spoke for public comment. She noted the reports shared the prior day, and hopes that the VA will look into treatments for demyelination. The consequences of toxic exposure over generations are extremely important and needs to continue to be discussed. She thanked the Committee for being the voice of the veterans.

David LaShell spoke for public comment. Every time he thought that the veterans were being forgotten, the Committee gave him a little more hope for the future. Presentations from this meeting helped to shed light on some new areas. His hope is stronger on this day than in previous meetings. He doesn't consider a farewell to the Committee members rotating off. The Committee has become a panel of experts, and the leaving members' jobs are not done. He hopes to hear more from those members in the future. He hopes to be able to touch base with Chairman Binns moving forward. He has stayed the course as a tenacious, unmoving force.

David LaShell recently was diagnosed with Type II diabetes. He wanted to mention dates specifically. The 1990-1991 Gulf War did have veterans exposed at the highest rates, but people were in theater until 1995. He personally fits into the after 1991 group of individuals, he looks forward to seeing more with Dr. Golomb's research study. He was also highly encouraged by the genomics research that Dr. Baldwin discussed earlier in the meeting. He thanked everyone.

Mr. Bunker noted the NGWRC.org sister site, the exact dates for Desert Storm, Desert Shield, and Operation Cease Fire are available. David LaShell thanked him for those details, and believes the dates will be very close to those he has seen.

Ed Bryan spoke for public comment. He had a few questions regarding the meetings. He wondered where they got the funding for the biomarkers. There is a need for an informational letter to all of the VA physicians, providing an update on current diseases and illnesses. Too many veterans are being denied claims. Physicians need to treat veterans. He is ten years behind the normal treatment process because of the VA. He cannot get treatment because he is a Gulf War veteran. The cause of death and death rate calculations for veterans need to be done. He thanked everyone for what they do. It has been a team effort. The leaving members will not be forgotten.

Chairman Binns noted the presence of Anthony Hardie at the meeting, a Gulf War veteran and former long-term member of the Committee, who would say some words to conclude the meeting.

Anthony Hardie began his meeting with a message of the need to respect each other. Public comment is a sacred time during the Committee. He encouraged members of the Committee not to have sidebars with other people while people try to have their voices heard during public comment. The Committee should continue to have a sense of urgency with their endeavors, which should never be lost. The purpose of the Committee should be to evaluate the effectiveness of all VA Gulf War research, which had been struck from the charter. The Secretary's attendance the day before was a big step in a good direction, but it will be a long and difficult road. Real numbers were heard the day before. Only 22,000 veterans' claims for Gulf War Illness have been accepted. The press release from the night before was very disappointing. He noted that the meeting during the second day was being held in Crystal City in a closet, and that it should be put back where it belongs in the main meeting room at VA headquarters.

Mr. Hardie asked the Committee members to remember that they are the voice for Gulf War veterans. GWI affects a third of GW veterans. It is physiological and not psychological in nature. A plan was developed in how to create treatment studies and plans. He asked that the VA focus on treatments in symptom relief in the short term but to develop treatments specifically designed to eventually treat the underlying condition. Many veterans have received band-aid treatments for their conditions. Understanding the underlying problem is a long way away, and he hopes that treatments for this will come.

The focus on causes is great, but people don't need to know what the cause is in order to look for and deliver treatment for their condition. The plumes affected probably most if

not all Gulf War veterans. Focusing on veterans in specific geographical areas is useful, but those lists have been found to have skewed data, so it might be good to keep this in mind. The VA Gulf War Task Force has been praised highly by VA, but it is not public, and it should be. Mr. Hardie's recommendation to make this public and include stakeholders was not carried out. Meetings need to be public, veterans need to be able to have a comment on what affects them. 250,000 are ill from GWI issues, only 22,000 claims have been approved. That is only about 1 in 10 people. He has had some claims approved, and others denied. The VA has a long way to go to show that they are really on the side of the Gulf War veteran. The VA has not been in touch with Mr. Hardie since his rotating off of the Committee. He hopes that the VA will stay in touch with Committee members rotated off moving forward, but he is not sure. He noted the CoQ10 treatments trial success, and he has been taking it. , He was walking with a cane 2 years prior, and is no longer depending on it.

He thanked Chairman Binns; he has been the best friend that Gulf War veterans have ever had. He has been completely trustworthy and upfront. He has traveled to Washington on his own dime to address Congress. He thanked the scientists for their efforts, and looked forward to working with them in other capacities. He also thanked the VA for the time he had as a member of the Committee. He specifically thanked Drs. Bob Jaeger and Victor Kalasinsky; he thinks that they are truly there to help. Being able to see a slide with the research, and the topic matter of the research is a real beneficial change from just a few years ago.

Chairman Binns could not think of a better way to conclude the meeting than with a veteran's statement. With that, Chairman Binns adjourned the meeting.