Research Advisory Committee on Gulf War Veterans' Illnesses

Committee Meeting Minutes
October 03 and 04, 2019

U.S. Department of Veterans Affairs
Washington, DC

Research Advisory Committee on Gulf War Veterans' Illnesses

Committee Meeting Minutes

I hereby certify the following minutes as being an accurate record of what transpired at the October 03 and 04, 2019, meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses.

Lawrence Steinman, M.D.
Chair, Research Advisory Committee on Gulf War Veterans' Illnesses

Attendance Record

Members of the Committee:
Dr. Lawrence Steinman, Chair
Ms. Kimberly Adams (telephone)
Dr. James Baraniuk
Mr. Brent Casey
Ms. Marilyn Harris (telephone)
Dr. Stephen Hunt
Dr. Katherine McGlynn (telephone)
Mr. Jeffrey Nast
Ms. Frances Perez-Wilhite (not present)
Dr. Carey Pope
Dr. Scott Rauch (telephone)
Dr. Mitchell Wallin
Dr. Scott Young (not present)

Special Guests:
Colonel Richard Gaard USA (Retired)
Ms. Barbara Ward
Mr. William "Bill" A. Watts (telephone)
Captain James N. Woody, M.D., Ph.D., USN (Retired)

Designated Federal Officer:
Dr. Karen Block

Committee Staff:
Mr. Stanley Corpus
Mr. John Rukkila
Ms. Marsha Turner

Invited Speakers:
Dr. LaTonya Small, VA ACMO, DC
Dr. Peter D. Rumm, VA Office of PDHS, DC
Dr. Katherine Hendricks, CDC, Atlanta, GA
Dr. Melvin Blanchard, Washington Univ., St. Louis, MO
Dr. Bennett Porter, Naval Hlth. Res. Ctr., San Diego, CA
Dr. Christopher Brady, VA Boston Healthcare System
Dr. Ian Robey, S. Arizona VA Healthcare System
Dr. Laila Abdullah, James A. Haley VA Hospital
Dr. Linda Chao, San Francisco VA Health Care System
Dr. Lisa McAndrew, WRIISC / VA East Orange, NJ
Dr. Albert Y. Leung, VA San Diego Health Care System

RAC-GWVI Subcommittee Members:
Dr. Lawrence Steinman, Chair
Dr. Karen Block, DFO
Ms. Kimberly Adams (telephone)
Mr. Brent Casey
Ms. Marilyn Harris (telephone)
Dr. Drew Helmer
Dr. Stephen Hunt
Mr. William "Bill" A. Watts (telephone)

VA Employees
Dr. J. Wesson Ashford, VA WRIISC
Dr. Ronit Katz, VA WRIISC

Veterans:
Ms. Helen Chandler
Mr. Ben Clawson
Ms. Andrea Freedom
Mr. Jeff Gang
Mr. Jeff Gracianette
Mr. Jimmy Guy
Mr. Randy Harrod
Mr. Ken Hiltz ?
Ms. Tracy Johnston (spouse) ?
Mr. Kirt Love
Ms. Denise Nichols
Ms. Sherry Thomson
Ms. Becky ????
Ms. Vanessa ????

Acronyms and Abbreviations

ACIP Advisory Committee on Immunization Practices
ACMO Advisory Committee Management Office
ADHD attention deficit hyperactivity disorder
ALS amyotropic lateral sclerosis
APOE apolipoprotein E
AVA Anthrax Vaccine Adsorbed
CA California
CBTi cognitive behavioral therapy .
CDC Centers for Disease Control and Prevention
CDMRP Congressionally directed medical research programs
CMI chronic multisymptom illness
Cmte Committee
CNS central nervous system
COL. Colonel in the U.S. Military
CSP Cooperative Study Program
Ctr Center
DC District of Columbia
DMV Department of Motor Vehicles
DNA deoxyribonucleic acid
DFO Designate Federal Officer
DoD Department of Defense
DSM-V Diagnostic and Statistical Manual (of Mental Disorders) (DSM–5)
Dr. Doctor
EDTA ethylenediaminetetraacetic acid
FACA Federal Advisory Committee Act
FDA Food and Drug Administration
GA Georgia
GW Gulf War
GWI Gulf War illness
GWVIB Gulf War Veterans' Illnesses Biorepository
Hlth. Health
HSR&D Health Services Research and Development (Service)
ICD International Classification of Diseases
JC virus John Cunningham virus
MD Medical Doctor
MILCO Millennium Cohort
MO Missouri
MPH & TM Master of Public Health and Tropical Medicine
MS Master of Science
NAD nicotinamide
NINDS National Institute of Neurological Disease and Stroke
NJ New Jersey
NR nicotinamide riboside
OEA oleoylethanolamide
OEF/OIF Operation Enduring Freedom / Operation Iraqi Freedom
ORD Office of Research and Development
PDHS Post-Deployment Health Services
PLOS Public Library of Science

Acronyms and Abbreviations
(Continued)

PON1 paraoxonase 1
PPAR peroxisome proliferator-activated receptors
PTSD post-traumatic stress disorder
Q fever Q or "query" for cause unknown in original description
RAC-GWVI Research Advisory Committee on Gulf War Veterans' Illnesses
RAND **r**esearch **and** **d**evelopment corporation
Res. Research
RNA ribonucleic acid
rTMS repetitive transcranial magnetic stimulation
SNOMED systematized nomenclature of medicine
SNP: single nucleotide polymorphisms
TDIU Total Disability Individual Unemloyability
Univ University
U.S. United States
VA Veterans Affairs
VABBB VA Biorepository Brain Bank
VAERS vaccine adverse event reporting system
VBA Veterans Benefits Administration
VHA Veterans Health Administration
VSO Veterans Service Organization
WRIISC War Related Illness and Injury Study Center

Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses (RAC-GWVI)

U. S. Department of Veterans Affairs

LOCATION: Hyatt Regency San Francisco Airport, Cypress Room A

1333 Bayshore Highway, Burlingame CA 94010

CALL-IN: (800) 767-1750; access code 56978#

WATCH ONLINE: http://va-eerc-ees.adobeconnect.com/racgwvi-oct2019/

AGENDA

Thursday, October 3, 2019

9:00–9:15	**Welcome, Overview and Introductions**	**Dr. Lawrence Steinman, Chair** **Research Adv Cmte on GW Veterans' Illnesses**
9:15–9:30	**Federal Advisory Committee Training**	**Dr. LaTonya Small, Program Specialist** **VA Advisory Committee Management Office**
9:30–10:00	**VA Updates on RAC-GWVI and GW Program Recommendations**	**Dr. Karen Block, Director, Gulf War Research** **VA Office of Research and Development**
10:00–10:45	**GWI and Infectious Disease**	**Dr. Peter Rumm** **VA Pre-9/11 Era Environmental Health Program**
10:45–11:00	**Break**	
11:00-12:00	**Anthrax Vaccine Adsorbed (AVA): Safety**	**Dr. Katherine Hendricks** **Medical Officer, Bacterial Special Pathogens Branch, Centers for Disease Control and Prevention**
12:00-1:00	**Lunch**	
1:00–1:45	**Birth Defects among Children of Gulf War Veterans**	**Dr. Melvin Blanchard** **Washington Univ School of Medicine, St Louis**
1:45–2:30	**Millennium Cohort Study**	**Dr. Ben Porter** **Leidos, Inc.; Naval Health Research Center**
2:30–2:45	**Break**	
2:45–3:30	**VA Biorepository Brain Bank: Gulf War Veterans' Illnesses Biorepository**	**Dr. Christopher Brady** **VA Boston Healthcare System, Boston University School of Medicine** **Dr. Ian Robey** **Southern Arizona VA Healthcare System University of Arizona**
3:30–4:00	**Committee Discussion**	**Dr. Lawrence Steinman, Chair** **Research Adv Cmte on GW Veterans' Illnesses**
4:30–5:00	**Public Comment**	

5:00 Adjourn

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AGENDA

Friday, October 4, 2019

8:30–8:45	**Introductory Remarks**	**Dr. Lawrence Steinman, Chair** **Research Adv Cmte on GW Veterans' Illnesses**
8:45–9:15	**Preclinical Evaluation of Nicotinamide Riboside as a Gulf War Illness Treatment**	**Dr. Laila Abdullah** **Research Biologist, VA Tampa** **Scientist III, Roskamp Institute**
9:15–9:45	**Effects of Low-level Sarin Exposure on Brain Structure and Function; and Cognitive Behavioral Therapy for Insomnia in Gulf War Veterans.**	**Dr. Linda Chao** **Professor of Radiology & Biomedical Imaging, and Psychiatry, Univ. of California, San Francisco** **Research Biologist, VA San Francisco**
9:45–10:00	**Break**	
10:00–10:30	**Improving Healthcare in Gulf War Veterans**	**Dr. Lisa McAndrew** **Research Scientist/Clinical Health Psychologist** **NJ War Related Illness and Injury Center**
10:30-11:00	**Improving Functions in MTBI Patients with Headache by rTMS**	**Dr. Albert Y. Leung** **Professor of Anesthesiology, VAMC San Diego**
11:00-11:30	**Committee Discussion and Recommendations**	**Dr. Lawrence Steinman, Chair** **Research Adv Cmte on GW Veterans' Illnesses**
11:30-12:00	**Public Comment**	
12:00n	**Adjourn**	

Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses (RAC-GWVI)

U.S. Department of Veterans Affairs (VA)

Thursday, October 3rd, 2019

Committee Meeting Minutes

Welcome and Opening Remarks

— Dr. Karen Block, VA Office of Research & Development and Designated Federal Officer, RAC-GWVI

Committee Chair Dr. Steinman called the meeting to order and welcomed committee members, speakers, and guests, and introduced administrative staff. Dr. Block continued and announced the meeting is a public meeting of the Research Advisory Committee (RAC) on Gulf War Veterans' Illnesses. She noted a quorum for this committee was present in person and on the phone and noted guidelines on how the meeting is conducted. She provided orientation to the conference room, meeting sign in, teleconference phone contact, and public comment. She welcomed new members of the RAC and thanked RAC administrative staff for pulling the meeting together.

Welcome, Overview and Introductions

— Dr. Lawrence Steinman, Chair, Research Advisory Committee on Gulf War Veterans' Illnesses

Dr. Steinman asked for introductions from the RAC Members sitting at the front table and on the phone. They each introduced themselves and briefly described their backgrounds. Dr. Steinman also introduced Marsha Turner, Alternate Designated Federal Officer for the RAC-GWVI. As the meeting sessions progressed during the day, Dr. Steinman introduced presenting committee members, speakers, and guests. He introduced Dr. LaTonya Small from the Advisory Committee Management Office who briefed the Committee on Federal Advisory Committee guidelines and ethics.

Session 1: Federal Advisory Committee Training

— Dr. LaTonya Small, Program Specialist, VA Advisory Committee Management Office

Dr. Small briefed RAC Members on providing successful recommendations as advisory committee members. She reviewed the Federal Advisory Committee Act (FACA) charter, committee structure, membership, terms of service, applicable regulations, and standards of conduct. She discussed what constitutes a FACA meeting and best practices for conducting meetings and making recommendations using a Smart Template. She described subcommittees and their relationship to the full committee and possibility of cross-committee collaborations with other VA Advisory Committees. Dr. Small requested that RAC Members read the VA Committee Member Handbook and commended the excellent work of the RAC-GWVI.

Session 2: VA Updates on RAC-GWVI Recommendations and GW Program

— Dr. Karen Block, VA Office of Research and Development, Senior Program Manager and the Director of the Gulf War Research Program

Dr. Block reviewed the Veterans Health Administration (VHA) Office of Research and Development (ORD) mission, services, vision, and funding. She provided an overview of VA-initiated and funded programs and active Gulf War research projects, outcomes, and translation from bench to bedside to develop effective treatments for ill Gulf War veterans. She reviewed VA Research as an intramural program

with investigator dual appointments and academic affiliations and she described cooperative studies projects, multi-center clinical trials, epidemiology studies, research leadership training, VA-DoD (Department of Defense) synergy and coordination, and ORD goals for fiscal year 2020. She reviewed: A) Development of a VA Research website as a project resource for Veterans and investigators. B) The Durham North Carolina Gulf War Research Resource Center (DRRC) to assist investigators in project recruitment and processes in addition for assisting Veterans in finding VA-vetted research projects of interest. The Gulf War Program manager will also utilize the DRRC to catalogue and collect consented Gulf War specimens and data to be deposited in a biorepository for research. C) The idea of recruiting Veterans to be actively involved in generating a research idea that they would like to see and supporting a pilot project of that idea. Dr. Block reviewed and discussed the three 2018 RAC recommendations: (1) Difficulties in moving forward to operationalize a pilot Warriors Health Network proposal; (2) Successful launch of the Project IN-DEPTH Gulf War illness sister protocol being conducted by the VA in partnership with the National Institutes of Health for investigative deep phenotyping of Gulf War Veteran health; and (3) Ongoing pursuit of VA modernization efforts for the new electronic health record to be developed as a tool for both clinical and research use.

In follow-up questions and discussion, Dr. Steinman reviewed factors for the lack of grant publications including forgetting to list the grant in publication acknowledgements and the immense time lag for peer-reviewed publications. Dr. Woody asked about resources to find VA-sponsored clinical trials and Dr. Block pointed out ClinicalTrials.gov and further review that she could do. Dr. Wallin and Dr. Pope inquired about data and prioritizing of research funding for projects to which Dr. Block further discussed the research review process and how budgeting is balanced out. Dr. Hunt reviewed that VA modernization of the health record includes big challenges to orient VA providers and Mission Act community providers with integrated information on a Veteran's military service and associated health risks as well as military culture and history. Marilyn Harris discussed the lack of awareness in the community as well as among VA providers about the Gulf War. Kimberly Adams suggested linking the electronic medical record to inform providers about Gulf War illness.

Session 3: GWI and Infectious Disease

— Dr. Peter Rumm, M.D., M.P.H., VA Pre-9/11 Era Environmental Health Program

Dr. Rumm provided an update on the types of infectious diseases associated with Gulf War I service. He pointed out that in addition to many toxic exposures that deployed Veterans experienced, some infectious diseases occurred but their incidence was lower than in previous wars. He discussed current registry surveillance programs available for Gulf War Veterans to complete and a new Military Exposures Newsletter recently published on the web. He reviewed the presumptive conditions involving Gulf War service and Gulf War illness and infectious diseases and discussed the Institute of Medicine 2007 Gulf War and Health Report, Volume 5, on Infectious Diseases and the RAND 2000 Report on Infectious Diseases pertaining to Gulf War Illnesses. Dr. Rumm listed those infections with sufficient level of an association to be a presumptive condition and those with limited or suggestive evidence. He reviewed the variant etiology of 12 cases of viscerotropic leishmaniasis and multispectrum/multisymptom illness of Q fever that occurred in 3 cases during the first Gulf War and in more post 9/11. He discussed the conclusion of the RAND Report that ruled out infections diseases as a major risk factor for illness in Gulf War Veterans but noted continuing attention to Mycoplasma infection as a cause Gulf War illness possibly through contamination of vaccines received by Gulf War Veterans. He also noted the squalene stabilizer component in anthrax vaccine had a suspected but unproven relationship with to symptoms of Gulf War illness. In addition, he noted investigations of various models or mechanisms of Gulf War illness that include searching for biomarkers or markers of inflammation. Dr. Rumm summed up that, "there is no scientific evidence to support infectious disease is a cause of widespread chronic illness in those deployed," but he emphasized that "it's based on the fact of the knowledge we have right now," which may change with a "little longer look."

In follow-up questions and discussion, Dr. Steinman asked whether pre- and post-deployment serological testing follow-up could be done on military personnel to verify virus exposures. Several comments were made: Dr. Rumm noted the National Academy and RAND reports did not find much evidence from serological testing. Dr. Porter noted military blood banks started by the late 1980s to collect sera in response to the HIV epidemic. Dr. Wallin stated the Department of Defense Serum Repository started in the mid-1980s in Silver Spring, Maryland, with to date over 100 million samples collected that would be a resource for an objective way to look at infectious exposures or even antibodies developing to vaccines. Dr. Steinman replied that straightforward rigorous studies could be done with this resource. Dr. Woody pointed out that studies of viral antigens and autoimmune disease are very fashionable right now and could be a connection that we could begin to look at. Dr. Hunt brought up the issue that just being in the military and being deployed is a health risk that probably changes your microbiome, and in this population, people are exposed to many kinds of assaults on their immunological system. Dr. Rumm recommended a future speaker should be an expert on inflammatory hypotheses and biomarkers. He closed by noting the launching this year of the VA and DoD Individual Longitudinal Exposure Record sophisticated database to track DoD and Veteran exposures combined with their health record.

Session 4: Anthrax Vaccine Adsorbed (AVA): Safety

— Katherine Hendricks, M.D., M.P.H. & T.M, Medical Officer, Bacterial Special Pathogens Branch, Centers for Disease Control and Prevention

- Michael M. McNeil, M.D., CDC Team Lead for the Vaccine Safety Data Link Team.
- Jarad Schiffer, M.S., CDC Chief of Microbial Pathogenesis and Immune Response Laboratory.

Dr. Hendricks, with Michael McNeil and Jarad Schiffer on the telephone line, presented background surveillance studies on anthrax and anthrax vaccine based on the Vaccine Adverse Event Reporting System (VAERS) and studies performed to follow up on specific non-DoD and DoD hypotheses. She described the Bacillus anthracis causative agent of anthrax and the epidemiology of cutaneous, ingestion, and inhalation disease. She explained the Anthrax Vaccine Adsorbed (AVA) vaccine and how it works to inhibit the formation and activity of the anthrax toxins and the surveillance of the most-common types of vaccine adverse events through VAERS since 1990 and through non-VAERS data since 2008. She reviewed the Advisory Committee on Immunization Practices (ACIP) guidelines on route of vaccine administration and long-term health effects in recipients. She noted short-term reactions comparable to other administered vaccines and in military personnel compared to the general population no increased risk of hospitalization and no association with chronic multisystem illness, long-term disability, or altered quality of life. She reviewed studies that confirmed squalene antibodies were not associated with chronic multisystem illness. She said additional surveillance studies reported through the Defense Medical Surveillance System concluded no increased risk in AVA receipts for type 1 diabetes; no association with long-term rheumatoid arthritis, systemic lupus erythematosus, and atrial fibrillation; and no strong associations between vaccination during pregnancy or risk of birth defects. In summary Dr. Hendricks noted no significant safety concerns since December 2008 based on VAERS or the published literature.

In follow-up questions and discussion, Mr. Nast asked whether the vaccine used in later studies was identical to the one given to Gulf War Veterans and Dr. McNeil and Mr. Schiffer confirmed the formulation has remained unchanged. Regarding the squalene issue, Drs. Steinman and Hendricks confirmed it's been investigated, put to rest, and it's just a natural product. Dr. Woody noted about review of squalene antibodies that other proteins or other antigens might be of concern. Ms. Turner noted Veterans often question that specific lot numbers of anthrax vaccine might have contributed to problems. Drs. McNeil and Steinman noted attentive FDA follow-up of adverse events for the same vaccine over a short period of time had not shown problems. Ms. Adams questioned whether there was a big difference in response to anthrax vaccine for deployed and non-deployed military in the in the review studies. Dr. McNeil replied that there was a healthy warrior effect with those deployed who received the vaccine often being actually healthier than those not receiving the vaccine. He also noted that despite problems with the VAERS passive reporting

system, safety for anthrax vaccine was verified in other large populations with many different health conditions evaluated in detail extremely thoroughly over some time.

Session 5: Birth Defects among Children of Gulf War Veterans
— Melvin Blanchard, M.D., Washington University School of Medicine, St Louis

Dr. Blanchard reviewed that after the 1991 Persian Gulf War the lay press reported birth defects among Veteran offspring, which prompted a survey of Gulf War Veterans and their families that suggested an increase in birth defects presumed due to chemical exposure, nerve agents, pesticides, and oil-well fires. He noted methods and results for multiple studies between 1997 and 2012 that sought to investigate the association between deployment and risks of birth. Although one study showed a difference between deployed and non-deployed Veterans in terms of birth defects, he noted results of five other U.S., Australian, and French studies did not show an increase in birth defects. He said these postal surveys and medical records or database reviews were not high-quality in-person studies; however, another Cooperative Study Program (CSP) investigation as part of the National Health Survey of Gulf War Veterans and Their Families involved structured pediatric history obtained by a research nurse with pediatric physician examinations of the children. The CSP study results did not include major birth defects but did "show that deployment of women in the Persian Gulf arena was associated with increased risk of minor birth defects in their offspring" with ptosis being the most-frequent minor defect noted. Although he said we don't really know the cause or mechanism of the defects, Dr. Blanchard postulated that some exposure could have affected the fetus or the germline, the sperm, or the egg. He noted the strength of the study was that it was a direct exam with a large sample and the limitations were that the sample was a fraction of those targeted, the defects in internal organs were not examined, only live births were reviewed, and no correlation was made between exposure and defects.

In follow-up questions and discussion, Dr. Wallin asked about further plans to review exposure and reported birth defects in deployed and non-deployed. Dr. Blanchard agreed it may be worth looking at the comorbid conditions in Veterans that reported birth defects. Dr. Katz commented that prior miscarriages would lead to a greater risk to have a baby with abnormalities. Dr. Blanchard said review of miscarriage risk would be an opportunity for future study. Dr. Block noted Veteran concerns about intergenerational effects on internal and reproductive organs and she asked about going back to look at these questions as additional major/minor defects. Dr. Blanchard noted the availability of the cohort and that it would not be difficult to track and examine them. Dr. Block inquired about the age of the kids in the study. Dr. Blanchard replied they were fairly young around 7 to 8 years old. Dr. Block also inquired about the level of the minor defect ptosis, whether the major deficit list included ADHD (attention deficit hyperactivity disorder), and the study limitations including review of developmental issues and internal organs. Dr. Blanchard replied ptosis was the major minor defect, ADHD was included in the major defect list, and a study is ongoing to address post-birth developmental issues. Dr. Pope noted a previous study in which rats injected with antibodies to acetylcholinesterase all developed ptosis. He confirmed further questions about the ptosis that it was bilateral, irreversible, and associated with sympathetic system nerve damage. Dr. Ashford noted that ptosis is the first symptom of myasthenia gravis, which is treated with pyridostigmine. He asked whether study follow up was done on children studied who had ptosis to check if their Veteran parents were more likely to have Gulf War syndrome? Dr. Blanchard answered he has a paper on follow up about Gulf War syndrome, did not link that with the kids, but may address this issue in a paper he is presently preparing. Dr. Steinman noted very rare genetic defects in cholinesterases can present like myasthenia with bilateral ptosis, and it may be possible to study cholinesterase gene mutations in Veterans. Dr. Blanchard replied we should still have blood on these Veterans and may be able to do that study. Dr. Katz noted and Dr. Blanchard agreed that birth delivery trauma may cause ptosis but would be less likely to occur with low birth weight. Dr. Hunt asked whether the pediatricians checking for defects had special training to identify defects and whether they were blinded or masked in their reviews? Dr. Blanchard stated the pediatricians were mostly university-based, were board-certified, and used a sheet with a number of different birth defects to look for.

He noted the pediatricians were not told who was deployed and who was not, but it may have been possible to break the blind if they were talking to the parent. Bill Watts asked how study participants were chosen and whether stillbirth, miscarriages, or premature births were listed? He also noted about the study that he was never contacted to participate, Veterans did not receive word to participate, and the study participants did not reflect some of the major military installations. Dr. Blanchard replied that a final random sample total of only 2,000 individuals was selected from deployed and non-deployed Veterans who were surveyed by mail, so it was not possible to survey all units. He summarized that there are more questions than answers and continued work is necessary to answer these important questions.

Session 6: Millennium Cohort Study

— Bennett Porter, Ph.D., Leidos, Inc.; Naval Health Research Center

Dr. Porter discussed how the Millennium Cohort (MILCO) Study emerged as a result of the problems within Gulf War Veterans at the end of the 1990s. He noted the MILCO study was established by the 1999 Strom Thurmond National Defense Authorization Act as a large prospective cohort study to detect reasons and cause for exposures as they happen. He said the study design links to DoD medical and administrative records as well as studies and future plans include links with VA records. The goal he said is to send surveys to participants every three years, four panels have been collected since 2001, and a fifth panel is due soon. Dr. Porter presented two studies looking at Gulf War Veterans: (1) Health status of Gulf War and era Veterans serving in the military in 2000 to describe the population of Gulf War and era Veterans enrolled in the Millennium Cohort study and compare the Millennium Cohort 2011 to 2013 survey and the 2012 VA follow-up study of a national cohort of Gulf War and era Veterans. (2) Prevalence of chronic multisymptom illness/Gulf War illness among Millennium Cohort participants, 2001 to 2016, to compare prevalence of CMI/GWI over time between Gulf War Veterans, era Veterans, and non-era Veterans. In the first study reviewed, Dr. Porter noted Gulf War Veterans self-reported much larger amount of exposures; were deployed in subsequent conflicts and presumably had additional exposures there; were a varied mix of ages; and were an enormous sample size of 9,000 Gulf War and 36,000 era Veterans. He pointed out prevalence rates of physical conditions between the VA study and Millennium Cohort study showed higher prevalence of physical conditions in the VA group than in the Millennium Cohort group and overall across the entire sample better health among Millennium Cohort participants than VA study participants. Dr. Porter summarized that all the different comparisons show Gulf War veterans are generally at higher risk for a large number of conditions. In the second study reviewed, Dr. Porter noted that the three groups were compared across time with a modified CDC definition and very stable effects: Gulf War Veterans are the least-healthy group; they have a higher prevalence of CMI and Gulf War illness compared to era Veterans; and although the comparisons remain parallel, the increase over time is substantial with people screening positive more and more over the years.

In follow-up questions and discussion, Dr. Wallin asked how was the Veteran study group was assembled differently than the Millennium Cohort? Dr. Porter replied the Veterans study that was collected by the VA is the third iteration of the VA study that collected 15,000 Gulf War Veterans and 15,000 era Veterans. Dr. Wallin questioned whether the cohort reported by Dr. Blanchard in the previous presentation was the same one and from the full military as well? Dr. Porter said that is correct except they looked from the roster files and sampled participants whether they were in the military or not when they collected their data. Dr. Wallin asked what percentage of Millennium Cohort actually is VHA or VBA (Veterans Benefits Administration) users? Dr. Porter replied we don't know yet and that's one of the first things to look at in connecting to the VA data. Dr. Baraniuk and Dr. Porter discussed confusion in the presentation about the vagueness in levels of symptom prevalence for population groups and how that's part of the problem of using the CMI definition and not including real complaints that Veterans have, which results in downplaying the importance of Gulf War illness. Dr. Steinman thanked Dr. Porter for sending prints of his recent manuscripts that are not available under open access. Dr. Ashford asked about whether the duration and number of deployments was considered among the three groups? Dr. Porter answered the number of

deployments was not included, only whether or not the Veteran had deployed at the time they completed the survey. Dr. Block asked for clarification whether graphs or tables showed that hypertension was not at higher risk for Gulf War Veterans and cancer was lower risk? Dr. Porter confirmed that's what was found, and hypertension may be discrepant with results of other studies because of the weighting of samples or designs of his two studies, and he said cancer may be discrepant because in both studies the result was largely fueled by skin cancer. Dr. Block asked whether Gulf War illness definition was looked at between the groups of deployed and not-deployed Gulf War Veterans? Dr. Porter replied this is probably the closest we've come in comparing the two groups, so we do find a higher prevalence in deployed Gulf War Veterans. Regarding increasing rates over time in Gulf War Veterans with Gulf War illness, Dr. Block questioned further whether, for onset in the Kansas and CDC definitions, the six-month or a year offset after deployment is a factor in missing some people that are showing symptoms later? Dr. Porter replied that a better understanding how these symptoms change over time would be a really helpful area of research because of later onset of symptoms, but he said he doesn't think his data really speak to that and we can't really say why.

Session 7: VA Biorepository Brain Bank: Gulf War Veterans' Illnesses Biorepository

— Christopher B. Brady, Ph.D., VA Boston Healthcare System, Boston University School of Medicine
— Ian Robey, Ph.D., Southern Arizona VA Healthcare System, University of Arizona

Dr. Brady presented an overview of the Gulf War Brain Bank and the outreach of the Bank with stakeholders. He described that a VA national amyotropic lateral sclerosis (ALS) brain bank was adapted in 2006 into The VA Biorepository Brain Bank (VABBB) that was further adapted in 2015 into the Gulf War Veterans' Illnesses Biorepository (GWVIB) brain bank with an associated post-traumatic stress disorder (PTSD) brain bank collaboration with the National Center for PTSD. He noted the GWVIB secures CNS samples with high-quality RNA and DNA that can be made available to investigators through a Boston operations and data coordinating center for recruitment and a Tucson processing center for tissue disbursement to investigators. Dr. Brady said the GWVIB broadly recruits enrollment through outreach to Veteran organizations' social media to all 1990–1991 Gulf War Veterans, regardless of whether they receive care at the VA, and at enrollment completes extensive health information data collection and medical history for demographics and physical features as well as a cognitive status review. He said enrollees are followed annually, or semiannually if their health is failing, and upon someone's passing the GWVIB arranges 24 hours a day and 7 days a week to make the tissue donation wherever they're at in any State and Puerto Rico through partnership with the National Disease Research Interchange, a national tissue recovery network. He noted the GWVIB is not just a brain bank but actually a living study with the value of the tissues being even greater when compared to the data collected while enrollees are living. He pointed out that with up to five years of follow-up data among the 65 Gulf War Veterans enrolled in the cohort so far, many are exhibiting high rates of exposure and symptoms, nearly half had Gulf War combat exposure, and 51% have chronic multisymptom illness by Fukuda criteria.

Dr. Robey presented details about how tissue samples are received, secured, delivered, and then processed in fixed and frozen format at the Tucson facility. He pointed out that GWVIB also has a blood collection protocol for a 21-milliliter blood draw that gets separated into frozen formats for DNA (gene sequencing and polymorphism studies), RNA (gene expression and micro-RNA studies), peripheral blood mononucleocytes (cellular studies), and stored plasma (blood protein and cytokine studies). He explained the protocol includes analysis of two types of genes: PON1 for the serum enzyme that detoxifies organophosphate poisons and APOE for the major cholesterol carrier that maintains lipid homeostasis in the brain and determines risk levels for vascular and neurodegenerative diseases. Dr. Robey described the rigorous review committee process to make sure tissue only goes to qualified researchers, and he reviewed the use of the biospecimen database management platform Tissue Metrics to catalogue tissue quality measures, demographics, disease characteristics, etc. He noted Tissue Metrics is HIPAA-compliant, fully

secure on a VA *intra*net website, and has a structured query language system that allows queries with multiple tables.

For a wrap-up review, Dr. Brady lamented that despite extensive national outreach, GWVIB enrollment thus far has been disappointing, perhaps in part because they are not a treatment study and are asking for a very sensitive donation. He noted GWVIB is a cost-effective scalable resource that can provide value added collaborations to current and future studies of Gulf War illness with long-term longitudinal follow-up, blood processing and storage, and CNS tissue samples.

In follow-up questions and discussion, Marilyn Harris asked where can families concerned about ALS go to get the research and updates on breakthroughs? Dr. Brady named several organizations including ALS Association of America, Muscular Dystrophy Association, ALS Therapy Development Institute, National Institute of Neurological Disease and Stroke (NINDS), VA caregiver program for family members struggling with ALS caregiver burden issues, and Target ALS Innovation Ecosystem for ALS research. Dr. Rumm added that Veterans get automatic service connection for ALS if they get it after they get out of the service. Kim Adams commented that the caregiver program is very specific about who can participate and could be based on an injury versus a disease process, so you must check to make sure you're eligible. She also commented as a Veterans legal advocate that every Veteran Service Organization and every VA facility should have information about this invaluable GWVIB program for Veterans. Dr. Steinman asked whether there is coordination with VA neuropathology centers to get tissue for research? Dr. Brady replied that arrangements are made with a VA as a primary source when it is available and alternative plans are made with a non-VA source if a VA is not available after hours, on weekends, and during holidays. Dr. Pope asked in the blood collection strategy what kind of anticoagulant is used? Dr. Robey replied that EDTA is used because it doesn't interfere as much with cytokine assays. Dr. Pope commented that because EDTA is a calcium-dependent enzyme it's going to be problematic because it pulls the calcium away and that irreversibly inactivates the enzyme. Dr. Ashford commented that the difficulties the GWVIB is having with recruitment are similar to difficulties with coordination throughout the VA. He noted that the Post-Deployment Health Service Program is trying to coordinate around the country with all the environmental health coordinators at every major VA site and with such coordination the GWVIB would have no trouble getting as much tissue as wanted. Dr. Brady replied that GWVIB actually did contact the environmental health coordinators; but unfortunately found the Gulf War is one of the many hats they wear, and sometimes it's hard to get to that. Dr. Ashford commented additionally that the WRIISC also had success in doing some genetic studies with 23and Me, which is very easy to use and cost effective. Dr. Block inquired about the attrition rate and how many donor enrollees actually give a brain at the end of the study? Dr. Brady noted for ALS that 95 % would give their brains and for Gulf War Veterans the refusal rate is very low. Dr. Wallin asked what turnaround time is from death to getting into the repository? Dr. Brady said it ranges from 12 to 48 hours and depends on the location of the death, the access to recovery specialists, and availability of transportation flights. Dr. Block asked if there is any kind of death that may not make the brain allowable to collect or not up to the standards for getting the kind of information needed for research studies? Dr. Brady replied that even after some type of anoxic event the tissue is still going to be useful and is graded with respect to types of studies that the tissue can be used for. He added that if someone has passed on for three or four days, recovery wouldn't be pursued, but that has happened only two or three times since his involvement with the study. Dr. Block asked whether quality RNA can be obtained from blood donated postmortem. Dr. Brady acknowledged that for surveys they try to get blood from living donors and they have considered the idea of postmortem blood but have not pursued it. Dr. Block asked whether any differences, such as Alzheimer's disease or any kind of pathology, have been noticed in a recent Gulf War Veteran who donated? Dr. Brady replied that for the recent Gulf War case, he was 69, had extensive pathology, and does seem to have some odd aspects. Dr. Block asked for more explanation about the GWVIB relationship with the Boston DoD consortium. Dr. Brady noted it is a consortium of a number of different groups involved with active recruitment and enrollment and if someone wants to conduct brain donation, they would be enrolled into the study, followed as would anybody else in the Gulf War Brain Bank, and the GWVIB would do the recovery and also do the follow-up. Dr. Woody asked if virus

infections, such as JC virus, are screened for in patient donors and live samples sent out. Dr. Brady replied specific screening is not done for anything like that and it hasn't been an issue in 10 years. Brent Casey asked how does the GWVIB know to go do a recovery? Dr. Brady replied when participants are enrolled the go through instructions and are provided a card with a 24-hour number to be called by the family. Dr. Steinman commented that people don't understand that the brain can be recovered, and the family can still have an open casket ceremony for the deceased. Dr. Brady noted people also think that because they are an organ donor on their license, that makes them automatically a brain done, and it doesn't. Dr. Steinman asked whether for ALS if spinal cords are also collected? Dr. Brady replied that the spinal cord is a necessary collection and maybe every 30th donation is either a short cord or skips a cervical, but he could not remember receiving a brain without a spinal cord.

Committee Discussion

— Lawrence Steinman, MD, Chair, Research Advisory Committee on Gulf War Veterans' Illnesses

Dr. Steinman asked Committee members to state their questions, comments, or criticisms.

Barbara Ward started the discussions by pointing out that the previous-year RAC-GWVI recommendation for which the VA did a nonconcurrence should be revised and resubmitted. She noted that based on her experience as a Designated Federal Officer for another Advisory Committee, a rephased recommendation and justification may be reinterpreted and get concurrence. She emphasized that if the Committee feels very strongly about something, then continue to push harder and harder.

Dr. Steinman replied that "committees that try to push the envelope a bit are quite valuable."

Dr. Wallin added that there was a lot of concurrence and support within our group and we put a lot of time and energy into pushing the envelope a little bit with the Warriors Care Network, and "maybe repackaging that in the context of our electronic health system may be a way forward." He noted the importance of linking the electronic medical record to other electronic resources and existing databases for the Millennium Cohort as well as the Gulf War and other Registries and using existing data in biorepositories and the DoD Serum Repository to answer research questions.

Marilyn Harris, in a later discussion, noted the proposed Warrior Network would provide specialization to get to everybody, which the Gulf War Registry is not able to do.

Dr. Steinman suggested emphasizing research into how care might be allocated rather than telling the system how it should do care would reframe the issue in a way that it might get accepted.

Dr. Woody continued and expressed appreciation for the elegant presentations with lots of really interesting and convincing data, and he noted the he does not think there is any doubt that Gulf War syndrome exists even though it is multifactorial. He asked whether Veterans actually know about the wide range of therapies going on in clinical trials for fibromyalgia, PTSD, migraine, etc., and is there a database they could easily access to inquire about participation in research being conducted near where they live?

Dr. Block noted ClinicalTrials.gov has that capability but is complex to use, and Dr. Woody confirmed that it's not simple.

Dr. Steinman asked about those getting care within the VA system whether there is a way to match people who have funded grants to clinic personnel who could actively tell about research or recruit for actual studies when people come to the clinic?

Marsha Turner replied, "you can't do a warm handoff at the VA" and clinic personnel can only give a flyer or information about a study and encourage their patient to call the study team. She noted, however, an example of quality success with Dr. Hunt at Seattle and his "Tell Your Story" study.

Dr. Hunt replied it is "an interesting paradox…being told stick to our lane…it should be about research. And at the same time, we're being told integrate research and clinical care and translational research, and how do we use research to help Veterans?" Continuing to address this issue, Dr. Hunt said there is no reason this could not be done in a more efficient and certainly more Veteran-friendly way and be built into

our workflow in primary care. He explained how the patient would come and have the registry exam, be plugged into care, learn about research opportunities, and get help with a compensation and pension claim. He summarized, "there is no reason this can't be done as kind of an implementation study for more Veteran-centered, Veteran-informed care. And we have a great opportunity now with Cerner to do a big project."

Committee members next discussed various support components for projects and grants such as increasing outreach communication with populations, putting ideas into grant requests for applications, reconsidering ways to manage grant funding disbursement, increasing social media promotion within a community, using newsletters to update participants recruited in a study, facilitating grant reporting mechanisms, and receiving effective feedback through research performance progress reports.

Col. Gaard asked whether a doctor of pharmacy participates as a member of the RAC-GWVI? He noted this would be a good resource to have on the Committee to give feedback on new medicines.

Dr. Hunt added that VA clinical pharmacists are doing so much around pain care, opioid safety, opioid use disorder, and treatments so it would be very important to include clinical pharmacists in the group.

Dr. Block pointed out how pharmacist support could help because sometimes Veteran research has been hampered when a researched drug was difficult to get as a formulation in the VA pharmacy.

Dr. Steinman summed up that we should think about other underrepresented parts of the VA that could include occupational therapy, physical therapy, and other domains we may not ordinarily think about, but a lot of great research could be done in those areas.

Dr. Baraniuk, on a new topic, suggested the need for inquiries into several additional aspects of Gulf War Veteran health such as: Can we get skin biopsies on the rashes in Gulf War Veterans and get the immunopathology of what's going on to give some real clues as to what's happening in this disease? What about the brain and determining cognitive function and the mechanism, prevalence, and progression to dementia as well as the cognitive components of fatigue, tiredness, and chronic pain? Are the coalition of negative emotion, depression, anxiety, and PTSD all different things or are they something specific for Gulf War in our patients? Is there anything neurologists can do through physical examination to help with diagnosis and help primary care people look at this as a real disease instead of just something in their patient's head?

Dr. Steinman wondered regarding getting brain tissue, are there any grants where induced pluripotent stem cells (iPSCs) are made from skin cells of Gulf War Veterans and then differentiated into neurons or motor neurons to see if differentiated skin cells behave in a way that's different?

Dr. Baraniuk replied that some DoD-funded grants are just starting with iPSCs.

Dr. Woody noted Dr. Pasca, a Stanford neuroscientist and stem cell biologist, is using iPSCs to investigate autism, and Woody suggested doing the same thing but in PTSD would be very interesting.

Brent Casey turned towards previous discussion about recruitment and primary care as well as provider lack of knowledge. He added his thoughts that although he learned about studies by paying attention to notices posted on WRIISC bulletin boards, he believes most Gulf War Veterans learn about studies through interaction with Facebook and other Gulf War Veterans. He suggested it would be ideal to have a database of Gulf War Veterans who are interested, willing, and wanting to be on a list to be contacted through an email for studies that come about.

Dr. Block noted that recruitment resourcing was a fiscal year 2020 strategic goal in her presentation.

Mr. Casey, in regarding the challenge of educating providers about Gulf War issues, gave the frustrating example of how 15 licensed physicians at one VA have zero knowledge or experience treating Gulf War health issues and they believe such issues are a "myth", but a single primary care provider at another VA is a source of definitive clinical care for Gulf War issues.

Dr. Hunt stated there is no reason recruitment can't be built into the intake process for every Veteran coming into the VA so that we learn about their military and deployment history and sort them into cohorts

for studies they are interested in. He said he really likes the statement by Rachel Ramoni, Chief Research and Development Officer for the VA, that VA data is a national resource and that taking care of Veterans is a national responsibility, not just a VA responsibility, which Dr. Hunt noted with the MISSION Act becomes even more evident. He emphasized that the research we are doing helps Veterans; however, they don't know that and if they are not involved, how would they know that?

Dr. Hunt went on further to note Gulf War Veterans have been having difficulties all the way along, they are still having difficulties, and even if other populations have similar symptoms, the Gulf War Veterans have more of them. He stated that for Gulf War Veterans "it is a health issue, not just a disease we're trying to figure out and treat, it's health impairments. People's lives are affected and they're not doing well." He asked how to integrate this knowledge into the whole health approach to Veterans' health care and the whole health issue of research not being disconnected from clinical care? He said he feels we are doing so much better than we were many years ago, but we are still not anywhere near where we need to be. Dr. Hunt emphasized supporting whole health implementation in the VA so that Gulf War Veterans get good whole health approaches that help them with health impairments, clinical care, and support for their families.

Jeffrey Nast reiterated the importance of informing VA doctors, especially the new ones coming out of medical school, of the need to be aware of the specific health issues of Gulf War Veterans. He noted he is not a scientist, but he is aware longitudinal studies are great, the brain bank is great, and tissue banks are good for science and for future generations; however, 30 years after the Gulf War we've got a ton of people that are suffering. He emphasized that it is most important now to stay focused on whatever we can do to get things into the clinics and to help people who are suffering and dying early.

Dr. Steinman, noting he thought the session had been very constructive and the comments were useful, asked for Committee members on the phone to continue the discussions and add their comments.

Bill Watts spoke that he is very much in support of creating an easy-to-get-to website that shows all the research currently going on.

Marilyn Harris reiterated the need to educate people about Gulf War illness and the Gulf War environmental exposures of Gulf War Veterans and the need to keep working to educate first-line primary care providers on what Gulf War illness is and who Gulf War Veterans are. She further emphasized the need to use technology to empower ourselves to reach more people through recording research talks and discussions with our brilliant researchers highlighting their research in video clips on our website.

Kimberly Adams said she likes Marylyn's idea for recorded research talks distributed to outpatient clinics so that information about Gulf War Veterans and illnesses gets to Veterans and their families and holistic research makes peoples lives better.

Dr. Block commented how we learned from the Veteran outreach sessions about dental issues that are not being talked about. She also requested Committee members to review copies of grant requests for applications she provided to see if they can be tweaked somewhat to get more emphasis on what research is important and what research you would like to see done.

Dr. Steinman made a final comment about the continuing value of the discussions and observations from the Veterans engagement sessions and review with Veterans invited to the previous June meeting. He noted the VA Secretary met with the invited Veterans, had a photo opportunity, and spent a lot of time with them, which was a very good indirect measurement of how much he valued that.

Public Comment

Participants in person and on the phone line made public comments covering a wide range of topics.

Sherry Comset, a reservist activated for Desert Shield/Desert Storm, related how she received 12 of 13 vaccinations given at one time and reacted so severely that she went to the emergency room that day but

was told the reaction was to poison ivy that had gone through her car's vents, which did not make sense to her as a medic at the time. In 2005, she said she went to the Cincinnati VA for a study, had every single issue on the Gulf War illness list, and just progressively got worse. She said she has had immunological problems that are very difficult to diagnose, and she had to quit working as a nurse because of the effects it had on her cognitively. She said she hopes the vaccination combinations as well as anthrax would be studied. She noted the deployed have more severe illness and more numbers have illness, but the non-deployed get scooted to the side because the weren't getting the other exposures.

Ben Klossen (Clawson?), Veteran, said he had the anthrax vaccine and asked whether any members of the panel had the anthrax vaccine personally and, if not, would they be willing to have it done?

Mr. Nast, a Committee Member, replied he had the anthrax vaccine but has had severe health issues determined to be related to Gulf War service and not pinpointable to anthrax.

Dr. Steinman, Committee Chair, replied that children and infants now as part of their vaccine regimen get multiple vaccines at once to protect against a lot of things and they do quite well in general.

Ben Klossen (Clawson?), further partially related comments that were cut off as a result of a bad phone connection. He related that he was a healthy individual who was shipped out with the military and served 6 years in the Army as a Black Hawk crew chief deployed to Kuwait. He said he received the whole series of shots plus booster spread and later experiencing severe joint and body problems that resulted in self-medicating with alcohol.

Denise Nichols, Gulf War Veteran and advocate, stated a list of issues to be addressed: Pre-9/11 data update has not been done in a long time and needs to be done. Help people who are not able to attend this RAC meeting in person, by loading to the RAC website the previous meeting minutes and the current meeting slide presentations so they can be followed online. Hold future RAC meetings at the Denver and Minneapolis VAs that have full facilities available. Post the agenda for the RAC meeting at least 30 days ahead of the meeting date so potential attendees know who will be speaking. Avoided in the future the unfortunate double scheduling today of the National Academy of Science meeting on respiratory problems of burn pits and oil fires and this RAC meeting that both affect Gulf War Veterans. Mandate education policies for providers to take training about VA.gov website information, the WRIISCs, exposures, and presumptives. Set up additional RACs for Veteran generational issues and spouses, and non-deployed illness issues. View my Facebook page where I post all the studies form WRIISC, CDMRP, and everything I find.

Dr. Block, Committee Member, asked Denise to send her the information about holding meetings at the Denver and Minneapolis VAs and forward any additional comments.

Dr. Steinman, Committee Chair, replied that presentations have been on the website, minutes posting is delayed for the need to be reviewed and cleared for confidentiality about communicating personal information, and an attempt will be made in the future to avoid double scheduling of meetings.

Vanessa (last name?), in the Air Force from 1997 until 2001, stated she was in a squadron with a lot of females all deployed all over the place, all received the anthrax vaccine as a common denominator, and starting in 2001 all have lupus, multiple sclerosis, fibromyalgia, chronic fatigue syndrome, cancer, or they're dead. She noted a survey she provided shows that from 1980 to the present day after exposures to a whole bunch of different things, all the women are suffering from the exact same illnesses. She said when she goes to the VA, they have absolutely no idea what I'm talking about if say, "Can you look into Gulf War syndrome?". She said she is tired of being told it is in her head and that being tired all the time is just because she is getting older. She commented the anthrax vaccine problem hasn't stopped, is out of control, and is going to get to a point where it can't be covered up any longer.

Kirt Love, disabled Veteran, stated he has been coming to the RAC meetings since 2002 and has for 17 years made presentations with hundreds of ideas and suggestions that have been ignored. He noted he suffered indignities, was left to suffer on the outside, and his own committee and recommendations were

ignored, kept from the Secretary, kept from everybody. He said he is tired, sick of it, nobody cares, and everybody is busy trying to create different variations of the story and he has every reason to be angry and no reason to be polite because he is not being treated politely. He stated, "this is about what the Veterans want. We're the customers, we deserve better….The way I've been treated here in Texas, I have the right to be angry."

Jeff Gracianette, Gulf War Veteran, stated he was part of a water treatment team in the Persian Gulf and upon his discharge had difficulties with mental issues. He related a long history of difficulties being treated at several VA facilities in California and Nevada, with little satisfaction except for quite a few years at Fort Miley in San Francisco where his records were readily obtained and reviewed through an open and effective online portal that none of the other facilities were able to access. He said he was wrongly accused of drug use and misdiagnosed with various mental issues, wrongly categorized as an uncooperative patient, openly scoffed at regarding having Persian Gulf syndrome, and totally unable to have his military records confirmed. He described the biggest issue was being bounced from VA to VA with nobody accountable to each other. He said, "they don't care. Every VA I went to said, 'Well, we can't do anything about that VA. Why? Because they're not part of our system.'" He summed up that everything said at the current meeting should be implemented, but the problem is that different VAs won't cooperate.

Adjourn

Dr. Steinman, Chair for the RAC-GWVI, adjourned Day 1 of the Committee meeting at 5:04 pm and announced resumption for Day 2 of the Committee meeting on Friday, October 4th, at 8:30 a.m.

Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses (RAC-GWVI)
U.S. Department of Veterans Affairs

Friday, October 4th, 2019

Committee Meeting Minutes

Introductory Remarks

— Dr. Lawrence Steinman, Chair, Research Advisory Committee on Gulf War Veterans' Illnesses

Dr. Steinman called the meeting to order at 8:30 am and reminded everybody that remarks in this meeting are publicly recorded. He introduced the first speaker for the morning, Dr. Laila Abdullah.

Session 8: Preclinical Evaluation of Nicotinamide Riboside as a Gulf War Illness Treatment

— Laila Abdullah, Ph.D., Research Biologist, VA Tampa and Scientist III, Roskamp Institute

Dr. Abdullah thanked Gulf War Veterans for their support in donating the blood samples that her research relies on. She reviewed translational Gulf War illness research being conducted at the Roskamp Institute and the efforts to make sure whatever is done at the mouse model level is reflected in what is going on with Gulf War illness to appropriately develop therapies. She described markers for Gulf War illness and mitochondria related pathology in Gulf War Veterans, including their bioenergetic deficits, reflected in low levels of nicotinamide (NAD) and interference in energy generation. She reviewed the use of mouse models to advance translational research focused on targeting the bioenergetics system and possible correction of deficits with nicotinamide riboside (NR) available as a dietary supplement nutraceutical. She said treatment with NR restored NAD levels and increased sirtuin expression to support mitochondria function and reduce inflammation and oxidative stress. Several parameters of inflammation and oxidative stress, she said, were elevated in brains of Gulf War illness mice and corrected after NR treatment. Dr. Abdullah said future directions include determining therapeutic relevance through clinical trials in Veterans with Gulf War illness.

In follow-up questions and discussion, Dr. Steinman asked Dr. Abdullah what is the most optimistic upside to her work? Dr. Abdullah replied that the clinical trial would move forward the development of proper treatment strategies with nutraceutical supplement. Dr. Steinman followed-up to question is there any downside and is the safety of the nutraceutical exemplary? Dr. Abdullah answered that the FDA has no objection and it is generally regarded as safe. Dr. Steinman commented whether there may be optimal dose beyond the nutraceutical dose or possible side effects with bigger doses? Dr. Abdullah replied about the importance to do the pilot studies to develop the right dose. A Committee member inquired about the mouse studies whether brain tissue or some other tissue was used? Dr. Abdullah replied mostly brain tissue. The Committee member inquired further about mechanisms of permethrin that was in the clothes that Veterans wore? Dr. Abdullah noted that once permethrin gets into the brain it can bind neurons to increase neuronal firing and disrupt neuronal neurotransmission as well as get deposited in fat storage to disturb lipid metabolism. She also noted her recent work showed it can be immunogenic, metabolites of it disrupt protein structures in the body, and mice and Veterans with Gulf War illness have antibodies that attack those modified proteins. Dr. Pope asked what is the connection between sirtuin and oleoylethanolamide (OEA)? Dr. Abdullah replied OEA targeted the peroxisome function, which is also related to bioenergetics, and sirtuin increases the expression of PPAR-alpha to regulate inflammation and dysfunction. Dr. Steinman noted about PPAR-alpha the dimorphism between males and females in regulating a lot of stuff with many of the factors that influence expression being controlled by testosterone. He asked about Dr. Abdullah's experiments in animals whether male response is compared to female response? She replied that some of those studies have been started and both male and female responses are being looked into. Noting that the

public comment in the previous day included anecdotes about many female-linked autoimmune diseases, Dr. Steinman stated it is enormously important especially in animal work to compare male/female differences. Dr. Block asked about control and Gulf War illness mice whether there is a statistically significant difference between 22 months and 5 months? Dr. Abdullah replied there is a slight progression with more of a learning phenotype and the memory not quite bad at 5 months but at 16 months the memory component shows up too, which is difficult to translate into Gulf War Veterans as they are aging. Dr. Block also noted weight loss also and asked if that was muscle mass or just not eating the food. Dr. Abdullah said there was no difference in food consumption, but it is definitely something that needs to be looked into. Dr. Block further inquired whether the swim test was done after treatment and what was the outcome after NR treatment? Dr. Abdullah replied that because it is a stressful scenario, it was done just one after start of treatment and we know at that timepoint there already is a very consistent phenotype, so we went ahead and did the behavioral testing. Dr. Block asked if any kind of Seahorse analysis was done on function rather than just acetylation of proteins and changes in protein content and binding? Dr. Abdullah said she definitely wants to get more into the mitochondria's energy generation and all other aspects. Dr. Hunt inquired whether neuropsychological testing with and without stressors was going to be done because of the relevance to Gulf War Veterans' experiences of many simultaneous exposures and immediate existential threat to their survival? Dr. Abdullah answered she hopes to expand this work and submit a separate proposal to better characterize the behavioral responses as well as the pharmacokinetics of the right dose in nutraceutical work.

Session 9: Effects of Low-level Sarin Exposure on Brain Structure and Function; and Cognitive Behavioral Therapy for Insomnia in Gulf War Veterans.

— Linda Chao, Ph.D., Professor of Radiology & Biomedical Imaging, and Psychiatry, University of California, San Francisco and Research Biologist, VA San Francisco

In her first presentation, Dr. Chao described neuroimaging studies on low-level exposure to organophosphate nerve agents sarin and cyclosarin in Gulf War Veterans exposed to the plume cloud from nerve gas demolitions at Khamisiyah, Iraq. She reviewed results from several studies on brain structural magnetic resonance imaging and diffusion tensor imaging. Dr. Chao summarized the effects of low-level sarin exposure in Gulf War Veterans as reduced gray matter volume throughout the brain, compromised macro (volume) and micro (increased mean diffusivity) structure of the hippocampus, reduced white matter volume throughout the brain, and compromised white matter (lower fractional anisotropy) and axonal (higher axial diffusivity) integrity.

In a second presentation, Dr. Chao described the relationship between Gulf War illness and sleep and reviewed a significant and positive relationship between insomnia severity and Gulf War illness severity. She showed study results indicating insomnia severity, subjective sleep quality, and Gulf War illness symptoms improved in Gulf War Veterans after treatment with cognitive behavioral therapy (CBTi). Dr. Chao summarized that CBTi is effective in helping Gulf War Veterans with insomnia achieve better sleep, Veterans' non-sleep symptoms improved along with improved sleep, Veterans appeared to be able to maintain the gains they achieved after completing CBTi, and CBTi may be a viable treatment for Veterans with Gulf War illness and insomnia.

In follow-up questions and discussion, Dr. Hunt asked what are the relationships in the hippocampus and subregions of the hippocampus related to psychological trauma and to sarin exposure for Veterans who had both? Dr. Chao replied that she can't speak to the interaction because in the study the Veterans with and without exposure were matched for psychological trauma. She noted, however, that her hippocampal finding is probably not related to psychological trauma and more related to exposure to organophosphorus nerve agents. Dr. Steinman asked whether there were any attempts to look at hippocampal findings with finer granularity by looking at wind direction and stationing of people exposed to the plume? Dr. Chao said she had not looked at that finely and she noted there was much skepticism about the plume models related to conjecture about the lack of measurements taken, location of people, and wind directions. Dr. Steinman

suggested going back to look at diffusion tensor imaging to see if there is a correlation to validate the model and give further weight to the data. He stated, if there is no correlation, maybe the model is wrong, and so you can't lose, but the Veterans could win. Brent Casey added that one thing for sure was that Gulf War Veterans who were in the exposed area did receive notification of verification from the Pentagon that their unit was exposed. Dr. Ashford commented about the inadequacy of determining the geography of actual troop movements, lack of symptoms in soldiers far removed from the plume, and that soldiers in the middle of the plume were much more afraid and took the pyridostigmine tables much more religiously. He added that he thought the Brief Pain Inventory used in Dr. Chao's study was a poor measure of pain and pain measurement was missing because of lack of a good pain measure. Dr. Chao replied that there were speculations about other exposures to nerve agents earlier in the war when chemical weapons facilities were bombed and many chemical alarms were activated. She noted research that found an inverse relationship between the frequency of Gulf War Veterans' self-reported hearing of chemical alarms and brain volume, suggesting a detrimental effect on brain volume that is not part of the plume modeling. Dr. Hunt asked if the research used a psychological trauma instrument other than simply PTSD diagnosis? Dr. Chao replied that lifetime stressor history was used and then the clinician-administered PTSD scale and PTSD diagnosis. Dr. Hunt commented whether nothing specific to deployment-related traumas was found? Dr. Chao said no, but at 10- and 15-years post-deployment many no longer met PTSD criteria or they had other traumas happen since deployment. Dr. Pope inquired about exposure levels and acute symptoms in the studies. Dr. Chao replied that levels of exposure were documented and followed in the Tokyo attack study. She said that although no acute symptoms were reported for Gulf War Veterans in the field there were anecdotal suggestions that a handful at ground zero did suffered acute symptoms. Dr. Pope questioned whether many Veterans reported they used their atropine injectors? Dr. Chao said it varied and she could not analyze that in a systematic way. Dr. Pope asked about the hippocampal studies in animals whether those were all relatively high dose and not low level down below where you would expect cholinesterase inhibition? Dr. Chao replied that in animal studies some were subacute or low levels of exposure, but the animals were directly injected and the dose they received was higher than whatever Gulf War Veterans would have been exposed to. Dr. Pope also asked whether somethings followed related to classic organophosphate mechanism of toxicity or something else not related to acetylcholinesterase inhibition? Dr. Chao said she thinks it does follow classic organophosphate toxicity. Dr. Block questioned what is the biological significance of small changes in decreased white and gray matter? Dr. Chao replied relatively young people were studied and found to have a 10-percent decrease in brain volume with less cognitive reserve that 10 or 20 years later may be a risk for neurodegenerative disease. A Committee member commented that exactly where the pathological attack occurred on the brain is not determined by the study findings and it is possible that more vulnerable structures in the brain stem did not adequately activate the cortex and led to decrease of white matter and gray matter in the cortex.

Session 10: Improving Healthcare in Gulf War Veterans

— Lisa M. McAndrew, Ph.D., Research Scientist/Clinical Health Psychologist, NJ War Related Illness and Injury Center

Dr. McAndrew reviewed the quality-or-care chasm that exists for Gulf War Veterans who are dissatisfied with their care. She described how implementing new treatments for Gulf War Veterans is blocked by barriers at the level of the patient, the provider, the clinic, and the healthcare system. She said, "it is not enough to develop new treatments for Gulf War Veterans, we also have to do research to make sure they receive these treatments." She emphasized that in the patient and provider encounter tug of war around symptom-based conditions like Gulf War illness, it is important to develop a shared understanding of what is happening. Dr. McAndrew found in an HSR&D study of medical encounters that Veterans receive better care when patients and providers work together to come up with a shared understanding. She said most important for Veterans was that a provider acknowledged and validated the Veterans' experience with Gulf War illness. Next most-important, she noted, was that the provider gave the Veteran specific recommendations for how to manage their Gulf War illness and defined a buffet of treatment options that

worked for the individual Veteran. Dr. McAndrew described the benefit of providing a modified evidence-based treatment and problem-solving therapy focused on reducing the tremendous disability of Veterans with Gulf War illness. She said surveys of Veterans indicated that when Veterans feel like they agree with their provider about their unique health conditions, they are more satisfied with the care they are receiving. In addition to developing treatments acceptable to Veterans, she said, we also need to develop treatments that providers are able to deliver and help providers understand military culture and deployment. Dr. McAndrew stated, "providers are baffled by Gulf War illness. They don't know what to make of it, they don't understand it." She found in interviews with doctors who saw Gulf War Veterans with Gulf War illness that 50 percent of the time the provider missed that the Gulf War Veteran had Gulf War illness. With further review of the medical records of Gulf War Veterans with Gulf War illness, she found only 31 percent of the time that Gulf War Veterans with Gulf War illness had a diagnosis consistent with that in their medical record. She showed additional data suggesting providers lack knowledge and said a way to help providers become more aware of Gulf War illness would be to teach them to look at service connection as an indication to think of Gulf War illness. She noted that the WRIISC has developed and disseminated trainings that have shown progress in educating providers; however, Gulf War illness is a very complex symptom-based condition and the resources needed to treat Gulf War Veterans in a short period of time to make complex behavioral changes may not be found in primary care. She stated a trial will be starting soon to see if a better model of care for Gulf War illness includes a specialist to work with the provider to improve care versus just providing education for providers. She noted further opportunity to overcome system-level barriers to improving care by facilitating the use of environmental health coordinators and clinicians and developing treatments directly available to Veterans. Dr. McAndrew said an application to deliver health coaching for Veterans with Gulf War illness is being developed to help them make lifestyle changes.

In follow-up questions and discussion, Jeffrey Nast asked whether required mandatory trainings would encourage or incentivize doctors to be educated and better providers? Dr. McAndrew noted just mandating trainings would not solve the problem in health care systems that have a lot of competing demands with providers doing a lot of trainings. Dr. Hunt observed that thinking beyond mandatory training we really need to change the whole culture of the VA by not only acknowledging Veteran-centered care but also building into initial on-board orientation of providers that the culture is about caring for Veterans, not patients, and that means connecting with Veterans as Veterans. He said to build in, perhaps through Cerner electronic health system modernization, greater system attentiveness to connecting with every cohort of Veterans to get their care at a level that provides good informed care beyond just referral to be treated by a specialist. Col Gaard suggested making cultural education a part of the continuing education that providers are required to complete. Dr. Ashford discussed that in addition to implementing a whole different culture, there is a need for post-deployment health clinics that primary care doctors could refer patients to for specific problems. To emphasize the difficulty in gaining an appreciation of Veteran issues sometimes belittled as being just in their mind, he summarized how tinnitus is a ringing sound in the head that can't be heard with a stethoscope but is nevertheless happening in the mind and is real to the person who has it.

Session 11: Improving Functions in MTBI Patients with Headache by rTMS

— Albert Y. Leung, M.D., Professor of Anesthesiology, VA Medical Center San Diego

Dr. Leung presented his research and clinician experience in working with Gulf war Veterans from a pain standpoint. He said that pain serves as a protective mechanism, but the vicious problem of continual pain has an impact on anxiety, mood, and sleep and if untreated can lead to significant diminished quality of life as well as suicidality. The focus of his talk, he said, was about the non-invasive brain neuromodulation method known as rTMS, which stands for Repetitive Transcranial Magnetic Stimulation and is a simple electromagnetic coupling event using electricity to generate magnetic pulses that stimulate the brain. Dr. Leung reviewed the Gulf War Registry participants medical records and noted the variations and disparity in the types and prevalence of exposures and pain documented by registry physicians in their clinical

assessments of the Veterans. He noted with no standard template or guideline for how to assess those patients, each physician came up with their own template and documented whatever they deemed important in their assessment. He suggested perhaps the group could make recommendations on clinical assessments. Moving on to review perception of pain in the brain, Dr. Leung thoroughly reviewed sites and pathways of the brain involved in pain modulation and their pertinence to neuroanatomical etiology and treatment effect of rTMS for suppressing neuropathic pain. He reviewed long-term benefits and rTMS studies and outcomes for migraine prophylaxis and for clinically feasible treatment in managing headaches in mild traumatic brain injury (MTBI) as well as depression and a few other conditions. For rTMS in Gulf War Veterans, he noted study results showed treatment relieved frequency of headache and benefited mood, sleep patterns, and some cognitive functions. He said in addition to helping Veterans with pain management, a multinational steering committee is moving forward with a treatment guideline and feasibility of doing this treatment with comorbid conditions such as depression. Dr. Leung said the task group on neuropathic pain definitely recommended the treatment for clinical implementation to include mild TBI-related headaches and studies are currently validating long-term efficacy.

In follow-up questions and discussion, Dr. Ashford commented that the WRIISC in Palo Alto has a project to get FDA-approved rTMS treatment of depression for Veterans throughout the country. To make a further anatomical comment, Dr. Ashford pointed out there are a lot of different areas of the brain involved in pain, particularly the brain stem, but if you lesion the frontal lobes, you really don't decrease the pain, it's just they don't care about it anymore. Dr. Leung replied that the brain is actually very dynamic when it comes to pain management, so it's not a one-model-fix-all type of thing. He noted that as an accessibility issue and for the need to have a conduit to get to the problem from a pain management standpoint, the cortex allowed accessibility to the whole pathway to stimulate the brain.

Committee Discussion and Recommendations

— Lawrence Steinman, MD, Chair, Research Advisory Committee on Gulf War Veterans' Illnesses

Dr. Steinman reflected that it was a very positive meeting and we need to start thinking of recommendations to bring to the Secretary.

Barbara Ward stated the Committee's charge to do research versus dictating care is challenge from a balancing standpoint because many of the issues raised. She said she liked the emphasis on providers knowing that the symptoms Veterans are experiencing are indeed true and not something in their head. She said looking at doing a clinical assessment template would be great and Cerner integration with the clinical medical record might be something to consider. The noted provider education is such a huge issue and unless VA really deals with that aspect the Gulf War Veterans will continue to struggle as far as treatment modalities go within the system.

Dr. Steinman replied that we will have to work hard to make sure in a clinical application that at least Gulf War illness and its manifestations are directly addressed somehow.

Marsha Turner noted that invited guest (such as Barbara Ward as a new but not yet certified new Committee member) recommendations can't be used today, only those from the Committee.

Dr. Steinman replied that is an important clarification, but recommendations have not been made yet until after reflection and we will take what was said under advisement.

Dr. Pope said he supports comments by Barbara Ward and one of the most interesting and surprising things he heard was that Veterans are getting "laughed at" or told that their problems are all in their head. He said he appreciates Dr. McAndrew's presentation on *Improving Health Care of Gulf War Veterans* because it showed how this kind of research can be done. He suggested research should be done on how training translates over to the perception of the Veterans' quality of care.

Dr. Steinman said there may be a good window to get a recommendation made to the Secretary about some kind of sound research on making sure that once Gulf War illness is addressed, the outcome of the study is going to be better. He noted in the end that research does lead sometimes to treatments. He related an

anecdote about how after a study comes out some people he takes care of state, "I wish I could be one of your mice."

Col Gaard stated he wished the general public could hear some of the information heard in the last day and a half, possibly through putting video clips online; he agreed with having an expert on Gulf War illness or special doctor at the sites; and with satellite VA clinics it becomes even more important to have the providers and pharmacists know about Gulf War situations and how to provide expertise with their advice.

Dr. Woody said there is misunderstanding of what actually happened in the Gulf, there is a lot of missing information as to what people were exposed to, and the Gulf War illness Veterans didn't have the credibility to begin with within the system. He stated one of the problems now is we're dealing with the mind disease, it's all in your mind, it's all in your head, and it's time we start thinking again about brain diseases. He related the medical history of pneumonia that was not understood fully until the microscope revealed bacteria and viruses and you could start to have a differential diagnosis, which is a concept that has not really moved into brain diseases like Gulf War illness. Animal models, he pointed out, show cognitive dysfunction, leading to biomarkers that could be validated in Gulf War illness Veterans. The biomarkers, he noted, lead to molecular mechanisms of disease, mitochondrial dysfunction affecting every cell in the body, and cholinergic mechanisms that will affect brain stem cellular regions. Molecular mechanisms, he concluded, are going to lead to new ideas of the mechanisms of these brain diseases. He stated the work of Dr. Chao is showing the importance of the hippocampus, in terms of white matter, as an important area to exploit to understand what happened and what we can do to fix those problems. He said the molecular mechanisms lead to treatment concepts in animals and then clinical trials and finally we moved from just questionnaires to being able to do something logical for Veterans. Dr. Woody said he is concerned about the possibility of progression to dementia, which should get out to the primary care people so they pay more attention to what Gulf War illness is and how they can help to stop this potential progression.

Dr Steinman said as we develop the recommendations, there are rich areas to develop, subtle things like diffusion with tensor imaging along with the pharmacology to develop treatments or the magnetic stimulation. He noted members of the Committee will help do the writing and he will be sending a letter and a lot of emails in the writing process, with areas to emphasize incorporating subjects discussed, the imaging, the therapeutics. He also said, regarding these meetings, in the future they will be held more regionally in the South and the North and other places away from the coasts.

Brent Casey asked why isn't there an ICD-10 code for Gulf War illness?

Dr. Hunt replied now there is SNOMED (Systematized Nomenclature of Medicine—Clinical Terms) and in our clinical encounters we can use Gulf War illness or Gulf War syndrome, or Persian Gulf syndrome as an identifier. But, he noted, the problem has been the case definition hasn't been entirely clear, and ICD codes are used for pieces—fatigue, myalgias, or memory problems—but not necessarily for the syndrome.

Dr. Block noted Dr. Helmer, from the New Jersey WRIISC, had some projects funded to look at case definitions, and Post-Deployment Health Services at the VA is working to come up with a clinical case definition.

Brent Casey inquired whether if having been seen at the WRIISC he can request the WRIISC to reach out to his provider to give him a heads up that I am a Gulf War Veteran? WRIISC personnel present responded yes but the provider may not listen to the heads up. Mr. Casey noted that he participated in Dr. McAndrew's problem-solving study that was very helpful to him personally and he recommended it to be helpful to other, as the research backs up.

Jeffrey Nast said to try to focus on things that can actually have a measured, quantifiable impact on the life of the remaining Gulf War Veterans. He said along with education of the doctors to recognize the symptoms, the cluster symptoms, maybe not with a formal ICD code but that this is going to help the Veteran with compensation and pension review for some type of very much deserved benefit. He added to focus on things that are emergent, can happen quickly, and have a positive impactful benefit as well as push the research to try to move these things along that show some promise. He also noted agreement with

spreading meetings around the country as much as possible to reach as many people as possible and provide a needed platform.

Dr. Block spoke of frustration about Veterans hearing that primary care physicians don't understand what Gulf War illness is even though it's been around for 30 years. She said we need to focus in our lane with putting the right evidence-based and implementation-based science recommendations in with the right wording for the change we really want to see to provide insights for best practical changes in care. She added that she really likes the biorepository idea because validation studies, such as the deep phenotyping study as a first-of-its-kind program-funded model, is going to shed light on Gulf War illness and be very hypothesis generating for future studies.

Dr. Steinman spoke of emphasizing focus on clinical research both from an understanding of pathophysiology but also therapeutics to go from therapies through devices to pharmaceuticals and include nutraceuticals that Veterans can order directly. He also said it also important to research repurposing drugs for pathways identified from research and adding people with pharmaceutical experience to the Committee is going to be important. He said emphasizing research on prosthetics could also be really important and we probably ought to get somebody on the Committee form the medical device side.

Dr. Block suggested she could distribute a document that shows all of the Gulf War-funded studies to date between DoD, VA, and Health and Human Services so everybody can look at least at the titles of these things and look and see what's been done, and maybe that will stimulate us to try something different or see where we've done a lot and what haven't we done.

Dr. Steinman replied to Dr. Block that her suggestion would also show a lot of things that are being done well. He then asked for discussion comment from any member of the Committee still on the phone line and turned the meeting to Public Comment after no responses to continue discussion.

Public Comment

Participants in person and on the phone line made public comments covering a wide range of topics.

Marsha Turner, Acting Committee Managing Director, announced to participants on the phone line that any points they would like to get across to the Committee they can send to the Committee email address, and we will make sure it gets out to the Committee. She emphasized that if it involves personal health information, it would be better to talk by phone. She said the Committee is all here and they're listening, truly care, and although they might not have an immediate fix to everything, they nevertheless want to hear you and be sure you know you are treated with dignity and compassion and respect.

Randy Harrod, Gulf War Veteran, stated one of his biggest fears is that all this research is going to go wasted if you don't get more Gulf War Veterans into the VA hospitals. He noted a lot of veterans get Persian Gulf license plates, and if we can partner up with the DMV, they have a list of everybody who's a Gulf War Veteran because they issue the plates. He said he is running across more Veterans that have prostate cancer and asked if there has been any more research into prostate cancer in Gulf War Veterans? He pointed out the Gulf War is the forgotten war, so Gulf War Veterans feel disrespected, and right on the VA's website, The VA says they prefer not to use the term "Gulf War illness." He said he understands why about illness terminology, because there are many symptoms involved, but a lot of veterans feel that it's demeaning their service or minimizing their service. Mr. Harrod inquired whether there is any difference in the effectiveness of treatment for sleep apnea, between Gulf War Veterans and non-Gulf War Veterans? Noting that the psychiatrists use the DSM-V as their handbook for diagnosing mental illnesses, he wondered if there is a way to make some type of manual, DSM manual or something like it for providers to use like a hand guide, that would be specific to Gulf War Veterans? He asked has there ever been a study of denial claims versus the suicide rate or denial claims—denied claims versus veterans dropping out of the VA health care system because of frustration? He told how he went through seven clinical trials of medication before getting a vagal nerve stimulator, and his psychiatrist pointed out unofficially that he's come across a lot of Gulf War Veterans that are immune or the medications are not effective with Gulf War Veterans versus non-Veterans, and Randy wondered if that has ever been researched. He said every VA

should have a Gulf War resource center that could be staffed even by volunteers, because OEF/OIF Veterans have their centers, and it would just take a small office, a resource center, where Gulf War Veterans could be educated locally with their own staff who know all the clinical trials and research. Now that Gulf War Veterans have carried these symptoms for many years, close to 30 years, he asked has there ever been any research done on how these symptoms change over the years? Do they get worse over the years? Do they cause something secondary over the years? Because the recent reports, he noted, are saying that Gulf War veterans are aging more rapidly than non-deployed veterans, as much as 10 years faster, so what happens with these symptoms as you age? With Gulf War Veterans having difficulty concentrating or remembering or having foggy brain, he asked has there ever been a study to see if attention-deficit disorder has been linked to Gulf War syndrome?

Andrea Freedom, a post-Gulf War Veteran—Northern Watch, Southern Watch, and Enduring Freedom—with three deployments, stated her primary care—co-managed care between the VA and the DoD—is at a point now where her DoD doctor has thrown her hands up because she doesn't know where to go. Andrea said her VA primary care says, "Oh, your DoD primary care can handle it." She noted that she asked for a referral to the WRIISC, and the WRIISC just said lose weight, stop taking muscle relaxers, no more pain meds. So, she asked, from a personal perspective, what can be done? Because there are no answers, we still don't know what's going on; however, she said, she is having all of these crazy symptoms. Andrea noted that she knows about the research trials that are being done currently for '90/'91 Gulf War Veterans, but what is in the works, if anything, for the post-9/11, post-Gulf War era Veterans from Southern Watch, Northern Watch, Enduring Freedom, et cetera? Andrea noted regarding this meeting that she absolutely was going to come, but realized that hotels were $300 a night, and there is absolutely no way she can afford that. She recommended, for meeting places in the future, to keep in mind that Veterans are going to have to pay their own way and that it should be a little bit more economical and affordable.

Dr. Block, Committee Dedicated Federal Officer, replied to Andrea that the Office of Research and Development does have a request for applications for post-9/11 research, many of the post-9/11 warriors have a lot of the same multisymptom illnesses that have been explained in Gulf War, and we know that there are a lot of military exposures that have similarities between the two groups. She said the nutraceutical and the mindful approach have done very well for these Veterans because these Veterans don't want to take another pill.

Dr. Jimmy, a neuroepidemiologist statistician, made comments on two concepts, one is latency and the other is heterogeneity. On the concept of latency, he stated, often we think on a time schedule that symptoms appear very quickly after exposures, but that often is not the case. He said he thinks with Gulf War, especially as folks age, that we'll start to see some symptoms that will appear as comorbidities, as recent comorbidities appeared. To give an example of this, he said he always thinks of the one-hit model, which is very much true for folks exposed to atomic bombs during World War II who have thyroid cancer many, many, many years later, with a latency period that can be quite long. He noted the same thing is true with skin cancer, squamous cell, basal cell skin cancers, for which the highest risk period is often exposure in the teenager years and then a basal cell cancer may appear when you're 50 or 60 years old. Something to keep in mind, he said, with Gulf War is that the latency period may potentially be quite long for different exposures. The other concept of heterogeneity, he sated, going back to the skin cancer example, is that someone with a fair complexion, like myself, is much more susceptible to skin cancer than someone that doesn't have a fair complexion. This is something, he emphasized, that we really must be careful of when looking at risk because one person may be much more susceptible than another person. He summarized that he thinks some of these answers will not come until we're really able to link up some of the PLOS (Public Library of Science) data with our survey data to find out who has susceptibility SNPs (single nucleotide polymorphisms), and that will help to guide drug developments because we'll have a better concept of what pathways are involved from a pharmacologic standpoint.

Helena Chandler, from the New Jersey WRIISC, Acting Director, stated there is clearly interest from the Committee around health services and how to improve health services, and a few people have said this is a

research committee. She said, she thinks one of the ways to integrate those things is there's a branch of research that's focused on implementation science, and so you could consider a call for that kind of implementation science, and the science would be around how to best disseminate, how to best get what we know out, whether that's education or interventions, and that would be a way that would be considered within your mandate, and you wouldn't get criticized for going outside your mandate, but maybe moving some of those things forward.

Jeff Gracianette, Gulf War Veteran, asked regarding research on brain stems, what if he doesn't show all the biomarkers in his brain, but according to his doctor he has Persian Gulf syndrome? What happens, he questioned, if he passes away and research that there's a particular marker becomes available to compensation and pension review? If they look, he questioned, and say, "He doesn't have the biomarker," does that mean that his wife's benefits are going to disappear? The comp and pen reviewer may react by saying, "Sorry, your wife is going to lose all of her benefits," or, "Sorry, you didn't have it, you have to pay all this back." He emphasized that is something to actually be looked at because comp and pen does do it. He said it's unbelievable that they would, but they do it. He related how he even got told that his permanent condition right now could be changed because he is trying to get a back date. His main VSO told him, "Be prepared for them to try to take your permanent condition." He said he just got a letter from Washington, D.C., that stated they did his claim correctly, but they didn't see the handwritten notes compared to the progress notes. He questioned how could they make a decision without talking to him first or looking at all the information? He pondered that with these current examples, what could comp and pen and these other organizations do with your research? The research being done, he said, also has to be put into perspective with comp and pension because comp and pension is his life, and they're the ones that choose what he can do and what he can't do with his life. He said researchers can only try to make his life better, which he realizes personally is all that can be done. According to the one doctor that he really trusted and his current doctor, that's all it is, it is quality of life today. He said he fully, fully loves the research being done and if one day a doctor looks at him and says, "You don't have Persian Gulf syndrome. The oil well fires did it to you," or, "One of these other things did it to you," he is fine with that, but he still has the condition.

Kimberly Adams, Committee Member, replied the problem that Jeff Gracianette is having if they're looking at potentially taking the disability is that the VBA can reevaluate your disability at any time. She said if for some reason they think or they've heard or they've read in your documentation that you're getting better, that will trigger generally a reevaluation of your benefits even though you know you're not getting better. It happens as often as you think, she said, so anything that may be in your documentation, such as if a doctor says they see some improvement, that could very well trigger a reevaluation of your comp and pen, especially if you are TDIU status, which is Total Disability Individual Unemloyability. She noted that sometimes it happens that a Veteran is not rated at 100 percent service-connected, but their benefits go up to 100 percent because they are called "deemed unemployable." Regarding research, on the other, she didn't know what to say about the collaboration between research and benefits, but she said she thinks they should do it simply because research is probably moving a little bit faster than the Benefits Administration wants them to move, therefore, that collaboration is going to likely be fully teethed. However, she said, it is a great idea because, especially with the Gulf War syndrome, it is being compensated, but it's being compensated slowly just like Agent Orange was compensated slowly, and just like Blue Water and any other compensation is going slowly, and Gulf War syndrome has to catch up to where the VBA is going to be—and that's the simple answer.

Dr. Block, Committee Dedicated Federal Officer, replied about research comments by Jeff Gracianette that when you're in a research study it is not connected to your medical records. She noted that research studies are de-identified, they convert information over to a number, and the study information is de-identified.

Dr. Ashford, VA WRIISC, said he would like to see us work a little more closely between the Office of Post-Deployment Health and the WRIISC programs and what the recommendations are of the RAC.

Becky, the spouse of a Gulf War Veteran who was there during OIF, but not Desert Storm, said her husband was at the War-Related Illness and Injury Study Center in New Jersey and it took approximately 2 years to get all the tests done to be able to go to the WRIISC. She said after their first try they were told, "We need a few more tests before we think we'll accept you." At that point, when Gulf War illness was suspected, and her husband was already diagnosed with chronic fatigue syndrome and IBS (irritable bowel syndrome), she said their problem was they still had to go within their VA system and educate these gastrointestinal docs and other docs that her husband might have Gulf War illness, and this is what we're looking for. She questioned once it's suspected, why isn't there a red flag within the system to say, "This is suspected, let's look for these sorts of things," because we know that fibromyalgia, chronic fatigue, IBS, cognitive behavior issues, and all sorts of other symptoms fall under it. She said when they returned from the WRIISC they were given a huge binder, 6 weeks later a 28-page document about all of her husband's results, and an appointment was set up with primary. She related how she spent an hour going through everything with a fine-toothed comb, typed up a 2-page outline, and had 27 different herbs and supplements that WRIISC recommended her husband to take. She said she only had an hour and they went through everything as best as they could. Since then, she said her health has decreased and she found out about this Committee meeting through the Kids and Spouses Unite website because she is now sick with a lot of the same things her husband is sick with. She noted her health has been declining, she has had three surgeries this year, and she has not been able to follow up on appointments for her husband. In falling through the cracks, she said one of the things that she would find extremely helpful when coming home is a micro clinic that has a GI doc, that has a primary, that has a rheumatologist, that has some people with nutrition, and that can all work together to help me with all these supplements. She said being farmed out, being hard to get to the VA, and spending a lot of time going from appointment to appointment, her husband is too exhausted and can't do it, so it would be great to have more of a team where they could come in and do what WRIISC does, where it's a one-stop shop and the providers really work closely. She also noted that out of the 27 supplements, the primary doctor was only able to prescribe three. She emphasized, this is why comp and pen is so important to us, because we need to be able to afford the treatments, and so far, she said, the nutritional dietary changes were the most successful in helping her husband's quality of life of life improve somewhat.

Denise Nichols, Gulf War Veteran and advocate, stated we need the Committee to think about making a recommendation to the Secretary to set up a separate advisory committee under his authority—he can do that, we don't need a law or anything—for spouses and the generational offspring. She said he should also consider that non-deployed Veterans need something because this keeps popping up and they need their time. For generational and spouse, she said, she just can't overemphasize that for them we need to have something separate from the Veterans and that would be an important recommendation for the Committee to include to the Secretary. And in addition to that, she added, we really need to look at unit studies and feeding into that pre-9/11 data of a current number of those alive and dead and what's the cause of death. She concluded that these questions come up all the time among Veterans on the Facebook page, these are things that can't wait, and these are things that need recommendations included from the Committee.

Adjourn

Dr. Steinman, Chair for the RAC-GWVI, adjourned the Committee meeting at 12:05 pm and announced the Committee will meet again in 2020.

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