Research Advisory Committee on Gulf War Veterans' Illnesses

Committee Meeting Minutes
August 8-9, 2016

http://va-eerc-ees.adobeconnect.com/p4zfizoopuf/
http://va-eerc-ees.adobeconnect.com/p6wjwrt873r/

Department of Veterans Affairs
Washington, DC

Research Advisory Committee on Gulf War Veterans' Illnesses
Department of Neurology
University of California, San Francisco
rac@ucsf.edu

I hereby certify the following minutes as being an accurate record of what transpired at the August 8-9, 2016 meeting of Research Advisory Committee on Gulf War Veterans' Illnesses.

_____

Stephen L. Hauser, M.D.
Chairman
Research Advisory Committee on Gulf War Veterans' Illnesses

Table of Contents

APPENDIX A

Presentation 1 – Victor Kalasinsky

Presentation 2 – Tony Wyss-Coray

Presentation 3 – Joe DeRisi

Presentation 4 – Stephen Hunt & Anthony Hardie

Presentation 5 – Jeffrey Moragne

Presentation 6 – Sergio Baranzini

Presentation 7 – Lorene Nelson

Presentation 8 – Adam Gazzaley

Presentation 9 – Wesson Ashford

APPENDIX B

Document 1 – Draft Recommendations for Discussion

Attendance Record

Members of the Committee:
Stephen Hauser, MD, Chairman
Kimberly Adams, JD (telephone)
James Bunker
Fiona Crawford, PhD
Marylyn Harris, RN
Stephen Hunt, MD
Nancy Klimas, MD
Katherine McGlynn, PhD (telephone)
Jeffrey Nast, JD
Frances Perez-Wilhite
Martin Philbert, PhD
Scott Rauch, MD
Caroline Tanner, MD, PhD
Mitchell Wallin, MD
Scott Young, MD

Committee Staff:
Jon VanLeeuwen, PhD, Managing Director

Designated Federal Officer:
Victor Kalasinsky, PhD

VA Office of Research and Development:
Robert Jaeger, PhD (telephone)

VA Office of Post-Deployment Health Services:
Peter Rumm, MD (telephone)
Erin Dursa, PhD (telephone)

VA WRIISC Directors:
J. Wesson Ashford, MD, PhD
Drew Helmer, MD
Matthew Reinhard, PhD

VA CSP Epidemiology Center - Durham:
Dawn Provenzale, MD
Kristina Felder
Mary Elizabeth Grewe

Acronyms & Abbreviations

ACA – Affordable Care Act
ACE – Adaptive Cognitive Evaluation
ADHD – Attention Deficit Hyperactivity Disorder
ALS – Amyotrophic Lateral Sclerosis
BBT – Body-Brain Trainer
CBT – cognitive behavioral therapy
CDMRP – Congressionally Directed Medical Research Programs
CFS – Chronic Fatigue Syndrome
CMI – Chronic Multisymptom Illness
CoQ10 – Coenzyme Q10
CPG – Clinical Practice Guideline
CpG – Cytidine-Phosphate-Guanosine
CRISPR/cas9 – Clustered Regulatory Interspaced Short Palindromic Repeat
CSF – Cerebrospinal Fluid
CSF2 – Colony Stimulating Factor
CSP – Cooperative Studies Program
DASH – Depleted of Abundant Sequences by Hybridization
DAV – Disabled American Veterans
DFO – Designated Federal Officer
DMDC – Defense Manpower Data Center
DNA – Deoxyribonucleic Acid
DoD – Department of Defense
DU – Depleted Uranium
EAE – Experimental Autoimmune Encephalomyelitis
EEG – Electroencephalogram
ELISA – Enzyme-Linked Immunosorbent Assay
FACA – Federal Advisory Committee Act
FDA – Food and Drug Administration
FY – Fiscal Year
FY – Fiscal Year
GI – Gastrointestinal
GW – Gulf War
GWAS – Genome-Wide Association Study
GWI – Gulf War Illness
GWV – Gulf War Veteran
HSR&D – Health Services Research and Development Service
ICD-10 – International Classification of Diseases-10
ICD-9 – International Classification of Diseases-9
ICU – Intensive Care Unit
IFC – Inter-Facility Consult
IMSMS – International Multiple Sclerosis Microbiome Study
IOM – Institute of Medicine
IRB – Institutional Review Board

LED – Light-Emitting Diode
MOU – Memorandum of Understanding
MRE – Meals Ready to Eat
MRI – Magnetic Resonance Imaging
MS – Multiple Sclerosis
MVP – Million Veteran Program
NBC – Nuclear, Biological, and Chemical
NICU – Neonatal Intensive Care Unit
OEF – Operation Enduring Freedom
OIF – Operation Iraqi Freedom
OPH – Office of Public Health
ORD – Office of Research and Development
PACT – Patient Aligned Care Team
PB – Pyridostigmine Bromide
PBMC – Peripheral Blood Mononuclear Cell
PCP – Primary Care Provider
PD – Parkinson's Disease
PD – Post-Deployment
PDHS – Post-Deployment Health Services
PDICI – Post-Deployment Integrated Care Initiative
PS-A – Polysaccharide A
PTSD – Post-Traumatic Stress Disorder
QB3 – California Institute for Quantitative Biosciences
RAC – Research Advisory Committee
RAC-GWVI – Research Advisory Committee on Gulf War Veterans' Illnesses
RDU – Rational Drug Use
RNA – Ribonucleic acid
SAC – Senate Appropriations Committee
SEER – Surveillance, Epidemiology, and End Results
SME – Subject Matter Expert
SNP – Single Nucleotide Polymorphism
SPF – Specific-Pathogen-Free
TB – Tuberculosis
TBI – Traumatic Brain Injury
TDF-11 – Tumor Differentiation Factor
TIM2 – T-Cell Immunoglobulin and Mucin Containing Molecule
UCSF – University of California, San Francisco
USC – United States Code
VA – Department of Veterans Affairs
VBA – Veterans Benefits Administration
VHA – Veterans' Health Administration
VINCI – VA Informatics and Computing Infrastructure
VISN – Veterans Integrated Service Network
VSO – Veterans Service Organizations
WRIISC – War Related Illness & Injury Study Center

Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses
Department of Veterans Affairs

LOCATION: San Francisco VA Medical Center
4150 Clement St, San Francisco, CA 94121
Auditorium (Building 7)

Call-in: (800) 767-1750; access code 56978#
Watch Online: http://va-eerc-ees.adobeconnect.com/racgwvi/

Agenda
Monday, August 8, 2016

8:30 – 9:00	**Welcome, Introductory Remarks**	**Dr. Stephen Hauser, Chairman** **Res Adv Cmte on GW Veterans' Illnesses**
9:00 – 9:45	**Update on VA ORD Gulf War Research Strategic Plan**	**Dr. Victor Kalasinsky** **VA Office of Research & Development**
9:45 – 10:30	**Blood Proteins as Indicators and Modifiers of Brain Function**	**Dr. Tony Wyss-Coray** **Dept. of Neurology, Stanford University**
10:30 – 10:45	**Break**	
10:45 – 11:30	**Research frontiers: Pathogen detection**	**Dr. Joe Derisi** **Dept. of Biochemistry and Biophysics, UCSF**
11:30 – 11:55	**Update on CMI Clinical Practice Guideline**	**Dr. Steve Hunt, VA Puget Sound** **Anthony Hardie, Veterans for Common Sense**
11:55 – 12:15	**FACA briefing**	**Jeffrey A. Moragne** **VA Advisory Committee Management Office**
12:15 – 1:15	**Lunch**	
1:15 – 2:00	**The Gut-Brain Axis: The Role of the Gut Microbiome in Neurological Disease**	**Dr. Sergio Baranzini** **Dept. of Neurology, UCSF**
2:00 – 2:45	**Research w/ Large Admin. Health Care Databases: Challenges and Strategies**	**Dr. Lorene Nelson** **Health Research and Policy, Stanford University**
2:45 – 3:00	**Break**	
3:00 – 3:45	**Committee Discussion**	**Dr. Stephen Hauser, Chairman** **Res Adv Cmte on GW Vetrans' Illnesses**
3:45 – 4:15	**Public Comment**	
4:15	**Adjourn**	

Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses
Department of Veterans Affairs

LOCATION: San Francisco VA Medical Center
4150 Clement St, San Francisco, CA 94121
Auditorium (Building 7)

Call-in: (800) 767-1750; access code 56978#
Watch Online: http://va-eerc-ees.adobeconnect.com/racgwvi/

Agenda
Tuesday, August 9, 2016

8:30 – 8:45	**Call to Order and Announcements**	**Dr. Stephen Hauser, Chairman Res Adv Cmte on GW Veterans' Illnesses**
8:45 – 9:30	**Technology meets Neuroscience - A Vision of the Future of Brain Health**	**Dr. Adam Gazzaley Dept. of Neurology, UCSF Executive Director, Neuroscape**
9:30 – 10:15	**WRIISC: A Resource for Veterans, Providers, Researchers**	**Dr. J. Wesson Ashford VA Palo Alto**
10:15 – 10:30	**Break**	
10:30 – 11:15	**Roundtable Discussion on Integrating Research and Care**	**WRIISC Directors and Res Adv Cmte on GW Veterans' Illnesses**
11:15 – 12:15	**Committee Discussion**	**Dr. Stephen Hauser, Chairman Res Adv Cmte on GW Veterans' Illnesses**
12:15 – 12:30	**Break**	
12:30 – 1:00	**Public Comment**	
1:00	**Adjourn**	

DAY 1

Welcome, Introductory Remarks

Dr. Stephen Hauser, Chairman of the Research Advisory Committee on Gulf War Veterans' Illnesses, called the meeting to order after technical difficulties were resolved. He welcomed everyone to the meeting and asked Committee members to introduce themselves. Present were Kimberly Adams (telephone), James Bunker, Dr. Fiona Crawford, Marylyn Harris, Dr. Stephen Hunt, Dr. Nancy Klimas, Dr. Katherine McGlynn (telephone), Jeffrey Nast, Frances Perez-Wilhite, Dr. Martin Philbert, Dr. Scott Rauch, Dr. Caroline Tanner, Dr. Mitchell Wallin, and Dr. Scott Young. Dr. Hauser indicated that there was a time conflict at 4:30pm, so the day's meeting would have to end by 4:15.

Dr. Hauser introduced the first speaker, Dr. Victor Kalasinsky from the VA Office of Research and Development.

Update on VA ORD Gulf War Research Strategic Plan
Dr. Victor Kalasinsky

Dr. Kalasinsky gave a brief overview of the research program at VA before focusing on the Gulf War Research Strategic Plan (2013-2017). Development of the plan began in January 2011and was approved at VA in February 2013. An update was completed in 2015, and another update is expected in 2017. He described the structure of the strategic plan with particular attention on the eight research focus areas in Section 5: (1) Symptomatic and Specific Treatments, (2) Databases and Continued Surveillance, (3) Case Definition, (4) Genetics, Genomics, Systems Biology, (5) Biomarkers, (6) Animal Models, (7) Coordination and Communication, and (8) Translation. He also showed some of the wording in the various sub-sections that could be considered for revisions.

Dr. Kalasinsky indicated the funding for the Gulf War program in recent years and showed a table of proposals received and funded. Dr. Crawford asked about the proposals reviewed in the most recent cycle. Dr. Kalasinsky indicated that only one of the 11 reviewed was deemed to be scientifically valid, so it was recommended for funding. He had contacted the other 10 investigators to discuss their proposals.

Active, funded projects were grouped by the focus areas in the strategic planto address those areas we have in the strategic plan. For treatments, complementary and alternative medicine, therapeutic drugs that are approved for other conditions, new ideas like LED irradiation are included. Exercise has been used for treating Gulf War Veterans for a long time. Another study that is very close to starting uses Coenzyme Q10 (CoQ10) in a multisite clinical trial based on pilot data published in 2014.

A number of studies are being funded to study biomarkers. The section numbers from the Strategic Plan were listed with the research projects to give an idea of what kinds of projects are being funded. Also listed were animal studies and projects that were

selected for funding. Some of them were supposed to start last October but were delayed for various reasons.

ORD supports two Gulf War repositories. In the first, brain and spinal cord tissue are being stored, and VA wants Veterans to sign up early so that VA can follow their health and obtain their medical records. The other is CSP 585, the Gulf War Era Cohort and Biorepository. In the pilot stage, over 1250 participants were recruited. Now in this phase 2 of the pilot, the CSP 585 staff are going to put together focus groups of Veterans and subject matter experts to find out how best to recruit Veterans to improve the research and clinical care. The first of the focus groups will took place the following day, August 9, in room 218. The idea was to get Veterans come to give VA their thoughts. Marybeth Grewe and Christina Felder hosted the focus group.

An Institute of Medicine report entitled "Gulf War and Health, Volume 10" which generated considerable discussion had been released in February. VA was close to finishing a response to the report. There were listening sessions where Veterans and other members of the public could share their opinions with VA. There was a RAC teleconference in June at which recommendations to the Secretary were finalized and approved. The Secretary was very pleased to get the RAC's letter and was interested in the recommendations. He was very positive about them. The Secretary's response will be sent back to Dr. Hauser, and he will most likely share it with the members. The final item to note is that VA works very closely with the DoD on Gulf War issues.

Dr. Hauser asked about for more details about CSP 585. Dr. Kalasinsky asked Dr. Dawn Provenzale, the team leader for CSP 585, to respond. For the pilot phase, mailed recruitment for people who use and not use VA for the healthcare was conducted. It include a survey of health history, health status, and Gulf War exposure questions. For the biorepository, phlebotomists went to the Veterans' homes to collect blood. There were 1276 people who signed up in the pilot. They are working with their IRB to come up with processes to share the data and specimens. The material will be available to VA and non-VA researchers. The biospecimens are DNA and buffy coats; RNA was not collected in the pilot. Gulf War information was part of the survey, and the consent form included a request to get VA and non-VA medical records. Researchers will have to go through the application process to get the materials. Dr. Hauser asked where the study will go next. Dr. Kalasinsky indicated that discussions on that topic were going. VA is trying to determine what went right and what went wrong with the pilot. Recommendations from the RAC would be helpful.

Dr. Klimas added that the study was designed to allow VA researchers to conduct genome-wide association studies (GWAS), but it is insufficiently powered to do that. The Million Veteran Program (MVP) should allow us to do GWAS, and the specimens are held in the same repository. Dr. Provenzale responded that she and Dr. Drew Helmer are study co-chairs for a GWAS, CSP 2006, the "Genomics of Gulf War Illness" that consists of participants who served in the first Gulf War and are also enrolled in MVP. They are users of the VA healthcare system. They are asking additional questions related to the Gulf War experience by mail. Deployed and non-deployed are

being contacted. It is a very complementary activity to CSP 585, just with larger numbers.

Dr. Hauser asked about the demographics of the CSP 585 cohort. Dr. Provenzale indicated that approximately 70% of them were deployed. They are further analyzing the data right now using the Kansas and CDC definitions. Dr. Klimas asked how many were sick. Dr. Provenzale asked if she meant sick with Gulf War illness or with other things, because the average age is 54 so they are starting to see cardiovascular problems and other conditions associated with aging. Dr. Klimas asked if the demographic breakdown was available, and Dr. Provenzale offered to send the slides she used at her last presentation regarding the characteristics of the cohort.

Dr. Kalasinsky added that the Secretary mentioned at the DAV meeting in Atlanta during the previous week that there were 500,000 people in the MVP cohort. It is halfway to the goal of one million. Dr. Helmer added that approximately 50,000 Gulf War era Veterans are in that MVP group, and approximately 30% were deployed. Dr. Hauser asked if buffy coats were prepared and frozen also. They were.

In referring back to the Strategic Plan, Marilyn Harris wanted to encourage privatization of goal number seven, Coordination and Communication with Federal partners, researchers, and the private sector. It is very important to her that Gulf War research continues and is not reduced in any way. Her feeling was that the best way to do that is to use the traditional business practice of partnering to foster good research and ultimately provide better care for Gulf War Veterans as they age. Dr. Klimas commented that if it took two years for the Strategic Plan to be approved last time, it seems like we are starting a little late. Dr. Kalasinsky indicated that it took two years for the initial plan to be approved, but the update in 2005 only took a couple months. If the plan is updated again, then there is enough time. If the desire is to discard the plan and start all over again, then there might be a time problem. It should be possible to have a plan ready for the 2018 to 2022 timeframe. Dr. VanLeeuwen reminded everyone that it was not necessary to decide everything right away, but the Strategic Plan can be an agenda priority for 2017 to put VA in a position to have one approved by 2018.

Dr. Hauser thanked Drs. Kalasinsky and Provenzale, and proceeded to introduce the next speaker. Dr. Tony Wyss-Coray is a Professor in the Department of Neurology and Neurological Sciences at Stanford University School of Medicine. He moved from UCSF to Stanford in 2002. He is also a Senior Research Career Scientist at the Palo Alto VA.

Blood Proteins as Indicators and Modifiers of Brain Function
Dr. Tony Wyss-Coray

Dr. Wyss-Coray is interested in cognitive aging and neurodegenerative diseases. He indicated that the approaches to studying the way our bodies change with age can be applied to any disease. The biggest challenge is figuring out the difference between healthy and sick brains. There are three things that affect the health of the brain: (1)

genes, (2) environmental exposures, and (3) aging. Traditional methods involve (1) neuropsychometric testing where you interview the patient to figure out what is wrong with the brain, (2) imaging tools, and (3) postmortem analysis. Only the postmortem analysis can provide information about the molecular changes in the brain, but that is only available after the patient has suffered from a neurological disease for many years. To study patients, it is necessary to look outside the brain, in the periphery.

With a cold you generally feel miserable. You may have a headache, feel sick, have memory impairment, and inflammation in the brain. Physical exercise, on the other hand, increases memory and cognitive function, gives you a positive outlook, triggers activation of memory pathways, and triggers the production of new neurons in the brain (neurogenesis). This suggests a clinical approach wherein cellular changes in the brain induce changes in the periphery.

This was revolutionized by the "parabiosis" model. In this procedure, two animals are surgically connected and allowed to share their blood supplies. The model was developed over 100 years ago but has been used more recently to look at stem cells for muscle development. In a recent publication, an old mouse with muscle damage was paired with a young mouse, and the muscle from the old mouse regenerated like it would in a young mouse. It appears that the stem cells are somehow activated to repair muscles, so there must be "factors" in the young blood that can help repair and regenerate old tissue. Other studies have demonstrated similar effects in the pancreas, liver and heart. Four labs have also shown that there can be positive effects on an aging brain. The blood connects all the different tissues in your body, so that is the place to look for the "factors."

They have used this concept to study cognitive aging. Decrements are normal as people age, but there is still a debate as to whether this is a precursor to dementia. As the body ages, it will influence all the other organs most likely through the blood. If the body ages, the brain ages. A big question was whether the blood ages as well, and there are differences between the blood of young and old people.

There are many different components of blood that can be monitored, but Dr. Wyss-Coray has focused on proteins. Of the tens of thousands of proteins, his laboratory is studying proteins specifically involved in communication. He referred to this as the "language of cells with the proteins being the words." There are protein factors that are recognized by receptors on other cells. The receptor triggers the cell to "survive," to be healthy, to make a daughter cells, to differentiate, or to die. Typical categories are cytokines, chemokines, growth factors, neurotrophins, hormones, and hormone-like proteins. Examples are interleukins, interferon, tumor necrosis factor, and growth hormone. By looking at these factors, Dr Wyss-Coray believes that they can capture information necessary to understand how cells "talk" to each other across the blood. So the problem is to figure out which proteins communicate with the brain to create new neurons. They have tried to identify the most relevant factors with the idea that the factors can potentially be manipulated in future therapeutic applications as well as for biomarkers. Dr. Wyss-Coray wants to go beyond the 10 or 20 well-known factors, and

characterize perhaps a couple of thousands of the secreted protein factors that can signal between cells.

He presented an example related to aging which can be applied to diseases as well. They measured 100 proteins in 300 samples from healthy individuals from ages 20 to 90 years by ELISA methods to try to discover a signature of aging. When they looked at the oldest in the youngest, they noted major differences in the levels of a third of these different factors ("biological aging factors"). Using statistical tools to figure out which factors are most sensitive to aging, they came up with an apparent age (a "biological age") of the patient. If the "actual age" or "chronological age" is plotted on the X-axis, and the Y-axis is the "biological age" calculated from their protein patterns, a 45° line would show perfect correlation of chronological age and biological age. The interesting features are the individuals who are outliers from the 45° line. For example, there was a 70-year-old person who was predicted to be only 45. The question that arises is whether this person is aging slower, is at lower risk to develop a chronic disease of aging, or is likely to live to 100 years old. Conversely, an individual who is less than 40 but has an aging signature of 65 potentially has a problem. Is he at higher risk of developing diseases of old age? This feeds into precision medicine, where specific treatments could be developed for individuals. Dr. Wyss-Coray is trying to expand the sample base and measure up to 1000 proteins, try the procedure in mice, refine it, and then predict the biological ages of patients.

The factors associated with maintenance of tissue development tend to go down as people get older, so what he had shown was a correlation. The question that arose was whether these factors are actually modulating the aging process. The parabiosis model allows blood from a young mouse to diffuse into an old mouse (equivalent to a 65-year-old human) after about five days. Even though the blood does not get to the brain, the old mouse increased neurogenesis and made three or four times more new neurons, simply by exposure to a young mouse for five weeks. There was increased activity of the synapses. There was more activation of the genes that are related to memory. There was improved memory and cognition, and reduced inflammation and microglial reactivity.

They could not use the parabiosis model to do behavior studies, however. For that, they developed a plasma transfer model. A small volume, 5% to 7% of the total blood volume from the young mouse, was injected every three days for 3 weeks into the old mouse. These mice showed improved cognition and some of the same molecular changes, demonstrating that there are factors in the soluble part of the blood, in the plasma, that are beneficial for an old brain.

Next, they wondered if they could take human plasma and inject it into an old mouse. Most mice would reject human tissue, but an immunodeficient mouse would not. They used human cord plasma, plasma from a 20-year-old, plasma from a 70-year-old, and saline (as the control). Saline and the 70-year-old's plasma both essentially had no effect. The young plasma improved cognition in the old mouse. On a test table where all the mice were trained for four days, four trials per day, the mouse was supposed to

learn where the escape hole was located. An old mouse had difficulty finding the escape hole. Another mouse, the same age, which had been injected with young human plasma every three days for three weeks (a small injection into the tail vein) showed very different behavior. The treated mouse looked for cues in the environment, and found the escape hole every time. The time it took to find the hole is the measure of their memory, so this suggests that something in the young plasma helps the older mouse. A three-month old mouse (equivalent to a 20-year-old person) required 30 to 40 seconds. The old mouse treated with young plasma was not that efficient, but he was much better than an untreated old mouse.

They have also tested this model in a neurodegenerative disease, Alzheimer's. Four groups of old mice were used: wild type injected with saline or plasma, and an Alzheimer's model mouse injected with saline or plasma. One cognitive test involved foot shock which tested whether a mouse learned that it would receive an electrical shock if it moved. A mouse with good memory would "freeze." Old mice with young mouse plasma freeze because they can remember the shock from the previous day. Those with saline injection or no treatment do not remember. With the young plasma treatment, there was a two- or three-fold increase in the freezing time. They have started a clinical trial at Stanford which should be finished by the end of this year. Patients with mild to moderate Alzheimer's disease receive one unit of plasma from young donors once per week. They are looking at cognitive testing, changes in blood, daily activities which involves speaking to caregivers.

Other studies are ongoing or in various stages of planning: progressive supranuclear palsy, Parkinson's disease, ALS, depression, and others. These are small trials to show proof of concept, but the work has to go farther.

Since there is not enough plasma to treat every Alzheimer's patient, their next goal is to identify the important factors, and the approach is to use proteomics as described earlier in people and mice. In mice, parabiosis can be used, and they can look at what has changed before and after treatments using a number of proteomic assays, such as luminex, aptomers, and antibody-based arrays, to measure the cytokines, chemokines, etc. They can now measure over 1000 factors, and they have tested a number of the factors in mice.

The young mouse suffers in this exchange with the old mouse in parabiosis. Brains become inflamed, they show less neurogenesis, and there was reduced cognitive capability. It was relatively easy to find old-age related factors, and they have injected these into young mice and thereby induced problems. It is possible to filter them out, but a better approach might be to use antibodies to block the receptors and interfere with the detrimental effects of these factors.

They are also trying to find rejuvenating factors to mimic the positive effects caused by young plasma. Factors like TDF-11, oxytocin, CSF2, and TIM2 improve cognitive function in old mice. Dr. Wyss-Coray and coworkers have blocked TIM2 to make old mice function better.

Taking an approach like this to a complex disease, like Alzheimer's, is incredibly difficult because you have to try to match clinical symptoms with the pathology. This is part of the reason we have not solved it yet in humans. We can solve it in mice, but translation has been difficult.

To address a condition like Alzheimer's, and perhaps Gulf War illness, you have to meet certain criteria. The population has to be very carefully characterized; otherwise, you have too much "noise" in your sample. It is equally important to have controls matched by age, sex, ethnicity, and exposure, in the case of Gulf War illness. The quality of the samples is important, as are sample collection and storage issues. Reliable and reproducible laboratory tests are required. The number of samples needs to be adequate, and the statistical methods needs to be appropriate. Finally, there needs to be independent validation by other research groups.

Developing an animal model allows you to test each aspect of a study. If you have small numbers, you can try to understand the biology of a signal which could allow you to validate a biomarker. Dr. Wyss-Coray measured 60 proteins in 20 mice and was fortunate that the top few biomarkers held up. That would be more difficult in humans because of the variability of the samples of the patients. In a recent study of Gulf War Veterans, there was a small number of patients, twice as many patients as controls, use of nicotine was not included, nor was there any mention of medications. If you do not match the population, it is much more difficult to interpret any findings.

Dr. Wyss-Coray concluded by saying that (1) factors circulating in the blood help the aging process and cognitive function, and (2) individual proteins replicate these effects and can be used as therapeutic agents, possibly even as biomarkers. Identifying individual markers improves the effect on the biology by giving you a target for patient care.

Dr. Klimas commented that the work he described was excellent. She went on to comment that in Gulf War illness, we know there is neural inflammation and some kind of degeneration, and we think that much of that came from toxin exposure. There are also some resources in the form of a biorepository, and she asked how the Committee might direct VA in conducting work like his that would result in treatments or markers.

Dr. Wyss-Coray commented that you need enough high-quality specimens and the funds to do the analysis. Most of his research in this area has been funded by philanthropy. He suggested that there needs to be a program where you can identify the individuals who can do the desired work and you put together a consortium of five or ten labs.

Dr. Philbert agreed with Dr. Klimas that the work was elegant. He wondered if they had done any work with other strains, like outbred mice which have a broader range of receptor functions. It seemed that they would be a better precursor for human clinical trials because you have a much more diverse group of participants. Secondly, he

wondered if they had tried lesioning the hippocampus to see if the factors can help that specific problem.
Dr. Wyss-Coray commented that they have used two strains of mice and it seems to work, but they have thought about using outbred mice. This is more expecnsive but they are planning to do it.

Dr. Wallin asked if there was a threshold age beyond which the blood is too old. Dr. Wyss-Coray indicated that they have not yet found that age. Their work has involved cord plasma and plasma from the equivalent of 20-year-old people. Since growth factors start to decline in the age range of 30 to 40, he would expect to see differences in that age range.

Dr. Crawford complimented Dr. Wyss-Coray and wondered how his work with changes in blood profile fits with the observation that people with Alzheimer's live for 40 or 50 years with those mutations before the clinical phenotype is expressed. She asked if patients would need continual transfusions or if it would be possible to identify the factors that were actually responsible for the changes.

Dr. Wyss-Coray said that they do not know how long these effects last and that they do not know the basis of this yet. It is not feasible to use a plasma treatment for the rest of a patient's life, so it is necessary to find the individual factors. They do not know the mechanisms, but one hypothesis is that they have changed the relative aging signature of the cells, so there are genetic and epigenetic factors, that turn on or turn off certain processes. When you reprogram cells to make a stem cell from an adult fibroblast, you wipe out all these aging signatures and you have an almost embryonic cell that can give rise to a young organism. They think that the treatments may remove some of the aging marks on the cells. So they reprogram some of the cells to become younger and their signature looks like a younger mouse – not as young as a 2-month-old mouse, but clearly different from an old mouse. Many of the genes that go up with age go down again, so there is something that they change at a very basic level in these cells so maybe it is possible to "reset the clock." You still age, but you change the relative level of aging to little bit lower. If you slow down aging you improve the healthy lifespan. In Alzheimer's, for example, it is estimated that if you can reduce the aging by five years, you can reduce the number of patients by 50%. And reducing neural inflammation can improve the other diseases that you want to study.

Dr. Hauser thanked Dr. Wyss-Coray and called for a 15-minute break.

When the meeting reconvened, Dr. Hauser introduced the next speaker. Dr. Joe Derisi is Professor and Chairman of the Department of Biochemistry and Biophysics at the UCSF School of Medicine. He published an article in the New England Journal of Medicine last year describing work that saved the life of a 14-year-old who had leptospirosis. Dr. Derisi is also the recipient of a McArthur genius award.

Research frontiers: Research frontiers: Pathogen detection
Dr. Joe Derisi

His focus is on a number of infectious disease related topics mainly working on Plasmodium falciparum malaria, but he planned to discuss neuroinflammation with the Committee because his work impinges on it. His interest is infectious diseases, specifically those of unknown etiology. With the exception of prions, every infectious agent has DNA or RNA, so studying DNA or RNA means you do not have to send out for extensive laboratory tests based on symptoms alone.

Most infectious diseases of unknown etiology have to do with encephalitis or meningitis. Fever, seizures, abnormal EEG, etc., make up approximately 20,000 cases per year in the US. As many as 6% are fatal, and for many of them the etiologies are never determined. The patients typically spend long, expensive stays in the NICU or ICU having many tests run. Many of the diseases are autoimmune rather than infectious, and treatments are very different for the two.

Dr. Derisi illustrated their approach with a few case studies:

The first case was a 29-year-old man with chronic headaches and double vision. He came from Nicaragua with no history of substance abuse. He had high pressure in the CSF with a high white count. This suggested an infectious agent, but he was negative for most assays. Tuberculosis meningitis was the diagnosis, but all cultures for TB were negative. He was treated for TB and improved a little, but eventually his headaches got worse and he had facial numbness. After 10 months he developed hydrocephalus with very high white counts. He did well on steroids for a while, then declined, and was put into the ICU.

When Dr. Derisi's lab was contacted, they drew CSF and sequenced everything. Ordinarily such sequences are 99.9% is human; in this patient, 3% was non-human. Their procedure is to remove all human sequences and compare the result to all databases for non-human sequences. The result was the pork tapeworm, and the brain was infiltrated. Neurocysticercosis probably accounts for a third of the epilepsy in the world, and is usually confirmed using brain MRI to visualize the worm scolex. Fortunately, albendazole can treat the condition, and the patient recovered.

In the second case, a 74-year-old woman with altered mental status was diagnosed with a urinary tract infection, but she returned with rapid vision loss in her left eye. MRI was most consistent with small strokes, so she was put on anti-coagulants and sent home.

The patient had an odd cough and was supposed to return to the TB clinic. She was wheeled in by her family, comatose. She was intubated and had additional brain imaging. Over a five-day period the MRI showed significant differences. There was inflammation and destruction of all parts of the brain along with hemorrhaging into the ventricle large abscesses. Antibiotics, anti-fungals, anti-parasitic medications were administered, but her white cells were very high, low glucose, and protein high. She

became unstable and eventually expired. When Dr. Derisi sequenced the patient's CSF, 25% of the data was non-human. All of the sequences belonged to one organism, balamuthia mandrillaris. There have only been 200 known cases of amoebic encephalitis since it was first identified in 1986. The etiology in this case remains unknown, although finding it in the vitreous of the left eye suggested that this could have been the portal of entry. Drugs have been effective in laboratory tests, but they have not been used in humans yet. The cost of the sequencing was considerably less than the hospitalization costs.

In the third case, a 14-year-old girl, already immunocompromised from a renal transplant, returned from summer camp and was unable to follow commands or speak. She declined into seizures, and delirium. She was treated with antibiotics and other medications without much effect. Laboratory tests were mostly negative, except for a positive test for coronavirus, a respiratory virus not known to cause neurologic problems. Imaging showed a lot of nonspecific findings. Dr. Derisi's team found West Nile virus, even though she was negative serologically. She had reported numerous skin of bites at summer camp. In follow-up serology, she was positive for West Nile. In this case, they used CRISPR/cas9 genome editing to cut then destroy human sequences in a programmable and cheap way to leave nothing but pathogen sequences. None of this sequences they wanted to look at were affected by this DASH (depletion of abundant sequences by hybridization) procedure.

The fourth case has to do with the eye, so Dr. Derisi counts it as part of the nervous system. A 40-year-old man, originally from a town near Stuttgart, Germany, with an 18-year history of chronic idiopathic uveitis. He had a three-day fever and rash in 1993 and developed uveitis in his right eye. He came to the US to get MS degree, but the uveitis continued to get worse and was treated in 2009. In 2012, aqueous was extracted from the eye, and the sequences were all from the rubella virus. The sequence maps best to a 1992 Stuttgart strain. In Germany, only girls were vaccinated - not boys. They can map all the mutations in the genome, replicating and mutating in the eyeball for 20 years. So there may be hidden reservoirs of rubella that are mutating in North America. Metagenomic sequencing tests like these are now offered at UCSF as part of the California effort to advance precision medicine.

Dr. Klimas commented that in Gulf War illness, there is poor cytotoxic function, evidence of low-grade viral reactivation, so we don't know if infectious agents are involved in perpetuating the problem. Some infectious agents have been found at various levels, but sequencing has been just too expensive until now. Dr. Derisi agreed that for a research study with a defined cohort, these tests can be done very efficiently. Dr. Klimas reminded everyone that the GWI repositories are blood related not CSF. Dr. Derisi noted that some organisms could be easy to see in blood. For neuroinflammatory diseases, however, it is not always easy to find infectious agents in blood. Dr. Klimas asked if they have normative data. Dr. Derisi's team has analyzed more than 700 patients, so they know what to expect in normal patients. Dr. Klimas wondered if Dr. Baraniuk perhaps had CSF samples.

Dr. Philbert asked if Dr. Derisi had been in touch with GAVI, the vaccine alliance, about organisms we should be vaccinating against. Dr. Derisi said that the vaccination program may not be concentrating on viral reservoirs, and the range of viruses that can get into the eye and replicate like this has not been studied. It is not known if there is something special about the eye that allows these replicated viruses to escape. From an occupational health perspective, Dr. Philbert wondered if ophthalmologists are aware of this problem. Dr. Derisi said that this issue needs to be addressed in case ophthalmologist should be using PPE.

Dr. Derisi indicated that there were difficulties detecting RNA in formalin-fixed tissue. DNA is okay, but frozen tissue is best for both DNA and RNA.

Dr. Rauch noted that Dr. Derisi did not talk about negative results. When dealing with something that is a non-biological toxin, was there some way of looking at the human genome and human sequence and realizing that it is not a biological load? Dr. Derisi noted that determining what is negative is an important concern. Not finding something might add to the diagnostic algorithm and help with a decision between autoimmune and infectious etiologies. Even though he did not mention it, they had also been looking into gene expression patterns, which are different for infectious and non-infectious etiologies. They do not have any examples of toxins in their data set, so they do not know what a toxin would look like, but he would be surprised if a toxin would look like a virus.

Dr. Hauser introduced Dr. Stephen Hunt from the VA Puget Sound who would be discussing the CMI clinical practice guideline (CPG) with assistance from Mr. Anthony Hardie from Veterans for Common Sense.

Update on CMI Clinical Practice Guideline
Dr. Steve Hunt and Mr. Anthony Hardie

Mr. Hardie is a Gulf War Veteran who has been active in Gulf War health issues for two decades. He was involved with passage of the 1998 legislation that authorized the creation of the RAC, eventually served on the RAC for about eight years, former Congressional staff member, executive of a state government veterans agency, and medically retired from the Army several years back. Currently, he is Director of Veterans for Common Sense, Chair of the programmatic panel for CDMRP, also Chair of the External Advisory Boards for the consortia at Boston University and Nova Southeastern University.

Dr. Hunt thanked Mr. Hardie for joining by telephone and indicated that he and Dr. Drew Helmer had been working on updating the clinical practice guidelines "Pocket Guide." Dr. Helmer passed them out to attendees. People online could download it. Mr. Hardie indicated that there is new Congressional guidance on this issue.

Dr. Hunt saw a Veteran the week before whom he wanted to tell the group about. He had diffuse pain, exposure to toxins and neurotoxins in the Gulf War, had been seen by

several providers in the VA. The consult came to Dr. Hunt because of pain. Gulf War Veterans generally have health symptom clusters, but they usually come in for a specific complaint. This patient was taking tramadol and hydrocodone, but VA providers were trying to steer away from opioid use for chronic pain. He was on low doses, but his pain was increasing. The patient had not had a Gulf War registry exam, he had paresthesias and needed further work-up. He met the criteria for PTSD, had a diagnosis of PTSD, fibromyalgia, and chronic multisymptom illness. It is important not to disregard the Gulf War symptoms while trying to deal with the other diagnosable conditions. Dr. Hunt recommended CoQ10 and mindfulness for symptom management, and considered sending him to the WRIISC. Congress had directed that Veterans should be treated. The patient said that he had been rated at 90% service connected illness. The clinical practice guideline was prepared to give providers guidance in treating Gulf War Veterans.

Dr. Hunt asked Mr. Hardie to describe the issues Veterans and Congress are concerned about. Mr. Hardie said that the Institute of Medicine (IOM) had called Gulf War illness (GWI) the "signature illness of the Gulf War," which affects one-fourth to one-third of Veterans. The IOM stated that GWI is not psychological, and that VA should use the term "Gulf War illness" rather than "chronic multisymptom illness" or other names. The CPG uses the term "chronic multisymptom illness." CMI was used not just for Gulf War Veterans, but also for OIF and OEF. This is a Federal interagency clinical practice guideline for DoD and VA, but possibly beyond these two agencies. The CPG recommends cognitive behavioral therapy, exercise, and psychotropic drugs for Gulf War Veterans. Mr. Hardie agrees with using psychotropic drugs for comorbid mental health conditions, but he is concerned that the CPG will be seen as recommending psychotropic drugs for GWI symptoms. He is also concerned that terms like "somatization disorder," "somatoform disorder" and related terms are used 52 times in the guide. The guide could be seen in its current form to be recommending a catch-all treatment for Gulf War illness. At a Congressional hearing back in February for the 25th anniversary of the start of the ground war, several experts testified that there were, "unproven and palliative treatments for" GWI, that CBT "is only palliative," and there was only a 1% improvement for GWVs. There was new Congressional guidance for health and benefits issues proposed for the FY17 appropriations bill, including 17 new provisos for Gulf War Veterans' issues. The Senate Appropriations Committee (SAC) expressed concern about VA's terminology and encourages VA to use term Gulf War illness as IOM has recommended. The SAC also recommends that VA revise and update the clinical practice guideline and include language that GWI is not a psychiatric disorder and instead focus on recent treatment findings. There is also guidance to VA to strengthen the training of providers and use the CDC and Kansas case definitions. The SAC suggests that VA assign a program manager for sleep disorders and sleep apnea, problems that affect 200,000 GWVs and OIF and OEF Veterans. The SAC continues to monitor VA's progress in dealing with IBS and other functional gastrointestinal disorders these areas and urges early interventions. These are just some of the provisos, but Mr. Hardie is pleased that Dr. Hunt and Dr. Helmer have taken the lead on the updates. He hoped that a revision of the pocket guide would be available soon, and ultimately a full revision of the clinical practice guideline.

Dr. Hunt thanked Mr. Hardie for presenting that summary. From his perspective, Dr. Hunt sees three important issues: (1) Nomenclature – the IOM shifted VA to the use of CMI. In the guideline, Gulf War illness can be looked at as a subset of CMI. (2) Making sure that it does not come across as a document that says Gulf War illness is a mental health condition. Dr. Hunt and other clinicians who treat GWVs regularly do not believe that it is, and it is important to make sure that a clinician does not come away with that impression. CBT is used for symptom management for mental health and other conditions. VA does not want the CPG to give the impression that GWI is mental illness. (3) Table 8 lists medications that are commonly used for depression. They are also used for global symptom loads. So the studies are looking at global CMI, not just Gulf War illness. While they are psychotropic medications that are used for depression and anxiety, they are also used for symptom management. That is why they are used for GWI, but this point needs to be very clear. The CPG lists comorbid conditions, so it might be that CMI can co-exist with psychological conditions, but not necessarily. Dr. Hunt wants Gulf War Veterans to be leading the way in how we communicate this.

Mr. Bunker pointed out that when Congress passed part two of the act that amended USC 1117 and described the chronic multisystem illness of unknown origin, it was clear that there is a multitude of chronic multisymptom illnesses. Diabetes and multiple sclerosis are chronic multisymptom illnesses, but they are diagnosable. He mentioned that 38 USC 3.317, amended in July 2003, listed exactly the intent of Congress, and it was Congress who made chronic multisymptom illness of unknown origin, so Congress has to change the section 1117 if it is to be called something else. Congress also defined in 2001 what can and cannot be chronic multisymptom illness.

Dr. Hunt said that in Table 1with the intent to get around this, they said it encompasses all those illnesses. VA just needs to make sure that the nomenclature is correct and not mental illness.

Mr. Hardie said that even with all the research at CDMRP, there is still no evidence-based treatment through Phase 3 clinical trials; some are moving in that direction. CoQ10 is one which is being started by VA in a multisite trial. Some others are out there that still need to be taken past the pilot stage, such as the carnosine study by Dr. Baraniuk, and a saline nasal spray study by Dr. Rabago that is near completion. Acupuncture for pain and fibromyalgia, and more recently for Gulf War illness, even though it is not clear why it works.

Dr. Hunt said that we are getting to the point where we may be able to have a CPG centered on Gulf War illness. Right now we are using the CMI CPG in a more general Way.

Dr. Klimas agreed with change in Gulf War illness terminology, so when she saw that the CPG used “CMI,” she disregarded it. She was also upset with some of the things in the decision tree. She also encouraged clinicians to use the Choice Act to allow

Veterans to get treatments not available in VA, because some of the things listed in the recommendations are not at her VA. They also do not have as much choice in their national formulary for prescribing medicines. She added that clinicians have to be careful about talking about comorbid conditions in treatment. She suggested that the table with columns for pain, fatigue, and GI needs an additional column for sleep.

Mr. Bunker remarked that there were a lot of medications on the list, and that providers need to be very careful about prescribing them. Every one of them has side effects that are among the kinds of symptoms that Gulf War Veterans are complaining about.

Dr. Hunt emphasized that the guide will suggest the use of non-pharmacologic treatments, but they do not want to prohibit using those that might be useful. Mr. Bunker said that his doctor will not prescribe any of those for him.

Mr. Nast complimented Dr. Hunt for focusing research on the clinical side. He wondered if there is a way to get an ICD-9 code for GWI.

Dr. Hunt said that VA has struggled since the whole issue of case definitions came up. He agreed that we need a code; give it a name and give it a code. Dr. Hunt closed by saying that he wanted the Committee to be aware of this activity and wanted encourage any and all input.

Dr. Hauser announced that the next speaker was Mr. Jeff Moragne, Director of the VA Advisory Committee Management Office, to discuss some of the important concepts in the Federal Advisory Committee Act (FACA). Dr. Hauser and Mr. Moragne decided to have the presentation during a working lunch.

FACA briefing
Jeffrey A. Moragne

Mr. Moragne introduced himself as the Director of the Advisory Committee Management Office, and as such, he works with all twenty-five of the advisory committees at VA that are guided by the Federal Advisory Committee Act (FACA). The FACA is a Federal statute that governs the establishment, termination, and management of Federal advisory committees. It was enacted to promote openness and transparency and to regulate the number and duration of advisory committees in the Federal government. FACA applies to any and all groups, with at least one non-Federal employee, established or utilized by a Federal agency to obtain advice or recommendations, unless an exception applies. Mr. Moragne indicated that at one time there were more than 8000 in the Federal government and now there were only about 1000. Each of those committees must be justified, so it is very difficult to obtain approval to establish new FACA committees. However, the Secretary was able to add a new FACA committee recently.

Mr. Moragne continued to explain that all FACA committees require a signed Charter that is filed with the GSA, a Designated Federal Officer (DFO), public meetings with the

agenda announced in the Federal Register 15 days in advance with an opportunity for the public to submit written comments, a balanced membership, and records maintained and available for public inspection. The FACA rules apply to all gatherings where substantive matters upon which the committee provides advice or recommendations are discussed. This includes "virtual" gatherings, such as tele- and video-conferences. The DFO is a VA employee who manages day-to-day Committee operations including approving meetings and meeting agendas, attending all meetings, and ensuring that meeting minutes are certified by the Committee Chair.

Mr. Moragne also indicated that Federal advisory committees can meet privately to conduct work that is preparatory to a meeting or to conduct and discuss administrative matters. If there are issues that require considerable preparatory work, the Committee can form a subcommittee to meet and consider a topic, but the subcommittee must report to the Committee at an open meeting where the topic can be discussed. Committee meetings may only be closed, in whole or in part, under limited circumstances, such as when discussing proprietary or personal information.

One issue that Mr. Moragne is frequently asked is whether Committee members may testify before Congress or speak with Congressional staff about Committee matters. He indicated that if a member is asked to testify, he/she may do so only in his/her personal capacity. Committee members do not have authority to testify on behalf of the Committee or the VA. Any testimony must make that point very clear. As a courtesy, VA would request that the member inform the DFO.

Mr. Moragne also discussed a member's term of service. The Committee charter must specify the length an appointment to the Committee, and long-standing VA policy limits a member to two terms (initial appointment and possibly one reappointment). New members are recruited in various ways, including announcements in the Federal Register. Members of the RAC were selected because of their special expertise and experience. VA has approximately 700 advisory committee members, and as members leave the Committee, VA would like those members to suggest other individuals who might be able suitable replacements. If members have recommendations for possible new members, they should contact Dr. Kalasinsky or Dr. VanLeeuwen.

One last point that Mr. Moragne made had to do with the "MyVA" program. VA alone cannot do everything that needs to be done, so strategic partnerships are part of the new MyVA program. He commented that cross committee collaboration is one way of ensuring that VA can avoid duplication and work more efficiently. Other committees have something in common with the RAC, and it is important for the commitees to interact. One easy way to do so is to invite the Chair or DFO of another committee to brief the RAC.

Ms. Harris referred to the most recently constituted committee and asked which one it was. Mr. Moragne indicated that it was the Secretary's favorite committee, the MyVA committee which started in April 2015. They meet quarterly, and he recommended that the RAC invite the MyVA task force to come describe the program changes that are part

of it. The Secretary is very corporate minded and has built structure that should outlast his time and his administration. In general, VA knows what does not work, and that is the basis for the MyVA program. So the VA is not going to tell a Committee what to think, but the Secretary has expressed a desire for recommendations from FACA committee to correlate to the MyVA principles.

Dr. Philbert asked whether FACA prohibited RAC members from testifying in front of Congress. Mr. Moragne indicated that VA lawyers give regularly scheduled ethics briefing, but for specific issues like giving testimony, it is always smart to contact the ethics lawyers whenever you have questions. He suggested contacting Dr. Kalasinsky, the DFO, or Dr. VanLeeuwen, who works very closely with Dr. Kalasinsky, to find out whom to contact in VA's Office of General Counsel. Dr. Philbert followed-up by asking whether he should contact VA if the FDA or some other agency were to call him. Mr. Moragne said that he should.

Ms. Perez-Wilhite commented that many disabled Veterans are small business owners, and there was a Supreme Court ruling which required that Veteran-owned businesses shall come first with Federal contacting. She asked if there was a committee working with VA on this issue. She knew that the VA has embraced this concept and wondered if there were ways in which the public could help with this. Mr. Moragne indicated that he was not aware of a committee specifically addressing that issue. It is not easy to form a new advisory committee unless the issues are distinctly different from existing ones.

Dr. Hauser thanked Mr. Moragne for his presentation and proceeded to introduce Dr. Sergio Baranzini, Professor in the Department of Neurology at UCSF. Dr. Hauser indicated that Dr. Baranzini has been working on three main topics: (1) trying to understand how genetic variants that are inherited differentially by all of us can be studied and how that information can be bridged with other types of information about the organism, thus creating a systematic biology approach, (2) genetic sequencing of the first female genome and the first disease genome, and (3) more recently, leading the understanding the human microbiome and how changes in the microbiome can influence our immune system.

The Gut-Brain Axis: The Role of the Gut Microbiome in Neurological Disease
Dr. Sergio Baranzini

As a geneticist, Dr. Baranzini became aware of common variances in DNA and how much they can contribute to a risk to develop common diseases. He has focused on multiple sclerosis, but the concepts apply to many other conditions. The genetic susceptibility to disease only explains part of the risk of developing disease; for example, for monozygotic twins will both develop MS in only 30 to 35% of cases, but if the risk were entirely genetic, this would happen 100% of the time. Among non-twin siblings, two will have MS only 5% of the time, so the rest of the risk must come from the environment. The problem is that it is extremely difficult to document everyone's environment – to remember what they have been exposed to or what they have eaten.

However, advanced DNA sequencing methods which are less expensive and quicker have made it possible to study any living organism anywhere. Dr. Baranzini's research team has used this technology to get a view of an individual's environment, especially in the gut. Since the environment can affect the brain, he referred to the gut-brain axis, or "neuro-gastroenterology: an emerging area of research." Research in this area has grown very rapidly recently. Some applications include multiple sclerosis and autism, as noted earlier, but now Alzheimer's, stroke, Parkinson's, and dementia are also being studied.

Dr. Baranzini gave a few definitions: Microbiota is the collection of microbial communities in a location, such as gut microbiota, skin microbiota, oral microbiota. Microbiome refers to their genetic material. Probiotics are live microorganisms which can be administered to patients. Prebiotics are fermented food ingredients that allow specific changes in the microbial communities.

He suggested that the enteric nervous system that governs the gastrointestinal system can almost be considered a second brain. It consists of 400 million neurons, which is similar to the number in the spinal cord. The human got microbiota consists of 10^{13} to 10^{14} microorganisms, and their collective microbiome accounts for 150 times genes than humans encode. Therefore the human metabolism represents a combination of the human and bacterial genomes.

There is a similarity of the communities that are collected from any given anatomical site. This early work was done at NIH when the human microbiome project was started in 2010. Although there is great variability in the organisms at any given site, the metabolic pathways are similar and stable. The microbiome changes with race, ethnicity, geographical locations, and diet.

The human-microbe relationship is very important to humans and the microbes. Of the microbes, 99.99% are non-pathogenic and help humans with immune responses, digestion, and amino acid synthesis. Humans need a healthy microbiome, particularly in our gut that in conjunction with our own genome keeps a healthy balance of pro-inflammatory cells that react against pathogens. The proportion immune-stimulating versus immune down-regulating bacteria needs to be in balance; humans need both. Any disruption to this balance may cause problems for the immune system.

Dr. Baranzini mentioned a few conditions where the gut microbiota is critical, in some cases just as an association, in some cases as a causal link. Obesity was one example. In the case of twins, one of whom was obese and one of whom was lean, bacteria from the obese twin caused germ-free mice to become obese, and bacteria from the lean twin caused the mice to remain lean. When these mice were co-housed, the mice receiving the lean-inducing bacteria were dominant over the mice receiving obese-inducing bacteria.

Obesity is associated with reduced bacterial diversity. Humans have 500-2000 bacterial species in the gut, and any factor that reduces the diversity can be harmful. This can be

seen in obesity, diabetes, MS, and according to Dr. Baranzini, that might be the reason that the connection to chronic disease exists.

Another example is the influence of the gut microbiota on cancer therapy. Elimination of the microbiota impairs the responsive of tumors to CpG oligonucleotide immunotherapy and platinum-based therapy. When the microbiota is eliminated, the therapeutic value of the anticancer drug is no longer there. Another example is resistance to cyclophosphamide in tumor-bearing mice.

There apparently exists a crosstalk between bacteria passed through the intestines and immune cells on the other side of the epithelium. Different messages may be sent to immune system cells that go into circulation. In theory, there should be no bacteria circulating in the blood that are pathogenic, but there may be very tiny amounts that go undetected in the blood that may influence immune responses. Similarly, bacteria may produce metabolites that cross the gut-blood barrier and they may cross the blood-brain barrier and go into the brain. That is why there may be a connection between the gut microbiome and certain neurological conditions.

Germ-free mice are bred and maintained throughout her lives in a sterile environment. When these germ-free mice are co-housed with specific-pathogen-free mice, the germ-free mice take on the characteristics of the SPF mice indicating that the horizontal transfer of microbes can modify behavior.

Bacillus ramosus changes expression of neurotransmitters in the cortex, hippocampus, and amygdala of the brain. Lactobacillus rhamnosus can determine the ways in which anxiety and depression are affected. This is a demonstration that communities that normally live in the gut can have an influence in the brain through their expression of neuropeptides-like molecules.

Children with autistic spectrum disorder have GI disturbances. Once the bacteria were sequenced, it was found that the bacteria are different in healthy children versus children with autism. It also has been shown that the toxins produced by Clostridium affect the behavior of most autistic children.

Lactation is affected by bacteria.

For an autoimmune disease like multiple sclerosis, mice treated with antibiotics are resistant to EAE, a disease similar to MS that recapitulates some of the symptoms of MS. If the mice do not have certain microbes, they cannot develop this condition. They have an impairment in their normal immune response which impedes the development of the disease, and this effect attributed to decrease in production of inflammatory cytokines and an increase in production of immunoregulatory cytokines.

The oral administration of polysaccharide A (PS-A) from Bacteroides fragilis protects mice from developing EAE, so it dampens the immune response enough so they can

modify the pathological development of this experimental disease. Now there is a company that is developing this and conducting a clinical trial on multiple sclerosis.

In another example, there is a model of spontaneous EAE. In this transgenic model, the mice are genetically engineered so the T-cells and B-cells of the immune system both recognize the same molecular shape, a shape that is similar to a protein in myelin. These mice will normally develop the disease within a certain time unless they are germ-free. If they have any microbiota, they start to develop the disease.

In a study of multiple sclerosis, a particular gene in Clostridium perfringens produces a protein with a similar shape to myelin. Immune cells recognize this shape and think that it is myelin, so they go to the brain, find myelin, and mount an immune attack there. In neuromyelitis optica (NMO), which is similar to MS, mounting an autoimmune response to that bacterium means mounting an immune response to the myelin in the brain. An article published in the Annals of Neurology showed that patients with neuromyelitis optica have an increased proportion of C. perfringens compared to healthy controls, and lots of patients with MS also have an increased proportion of C. perfringens.

In his laboratory, Dr. Baranzini and his team have been looking for the potential link between MS and the gut microbiota. They wanted to see if there was autologous stimulation of peripheral blood mononuclear cells (PBMCs) from an individual with his/her own fecal bacteria in a dish. Blood cells from untreated MS patients were cultured with extracts of their own gut bacteria. They had a reduced ability to control inflammation even though there were only minor differences in the microbiota compared to controls. When they looked at the presence of individual bacterial species, some were elevated and some were reduced. For example, there was a statistically significant increase in the proportion of Acinetobacter in MS patients compared to controls. All of the controls are people in the same household, typically spouses, who ate the same food, so they were the best possible controls.

The organisms that increased in MS were known to have a reduced ability to mount an immune regulatory response, and this is consistent with their findings. The species that were increased in multiple sclerosis patients also produced more of an inflammatory response when cultured in vitro. Those that were relatively depleted in MS patients were the ones that in vitro contributed to impaired immunoregulatory response.

They were able to demonstrate that there was an association between the microbiome and MS patients, but Dr. Baranzini also wondered if they could show a causal linkage. When they transferred microbiota from the gut of an MS patient into germ-free mice and then induced EAE disease, they had very aggressive disease – much more aggressive than in mice that were fed bacteria from healthy individuals, or those mice that were kept germ-free (controls). This confirmed their original ideas.

They were able to attract funding from DOD, from the National Multiple Sclerosis Society, and a big part from philanthropy to create the International MS Microbiome Study (IMSMS). The goal is to get 2000 patients and 2000 controls to do a genetic

study, a proof of concept study, and immunological study in a reproducible statistically-significant way. The ultimate goal will be for the IMSMS to come up with therapeutic options, to transfer microbiota, or identify particular molecules that will be beneficial to people with MS. Gut microbiota could have a profound effect on the pathophysiology of the disease. For this Committee, it would be important to determine the connection between microbiota and symptoms like chronic pain, depression, fatigue, and so on.

Dr. Klimas commented that this work was very interesting and that she had heard of a case where Tourette's syndrome was linked to Strep. And while it was not the gut microbiome, it was an infection with a consequence in the brain. She asked if it is better to have big diversity or low diversity in the gut microbiome. Dr. Baranzini indicated that increased diversity has been associated with healthy status in most studies. Dr. Klimas said that she prescribes Xifaxan for irritable bowel to eradicate C diff and perfringens, but she wondered if she was also going to eliminate the necessary diversity in the microbiome. Dr. Baranzini suggested that part of the increase in the prevalence of chronic disease in the past century is probably due to less diversity possibly linked to the overuse of antibiotics. Dr. Klimas asked if there were any probiotics or prebiotics that enhance diversity. Dr. Baranzini was not aware of any. A lot of probiotic studies that have been published did not support a large effect on the microbiota as a whole, so it is important to keep doing studies into reducing certain classes of microbes but not others. And these have to be big studies because small studies can be confounded by probiotics, diets, and other therapeutics.

Dr. Hauser asked how it might be possible to identify in 2016 a signature from something that happened in 1991. He asked if Dr. Baranzini could think of a way that microbial genomic analysis might contribute to this and how many individuals would be required for such a study. He also asked if the study should consider any Veterans with related multiple symptoms or focus on fatigue or pain or irritable bowel, all of which are probably pro-inflammatory activation. Dr. Baranzini said that he would not know how to power a study like that. It certainly would not be a 50 case, 50 control study. There are too many variables that can contribute to the diversity of microbiota, and it is necessary to be sure that the right effect is being studied. On the other hand, this provides an opportunity for the Committee to think about the gut microbiota as a proxy for the environment. For the symptom issue, it would be necessary to define the phenotype as tightly as possible. For better outcomes and better statistical data, one or two of the main symptoms would be appropriate, but not the full symptom list. The studies would have to have large numbers of participants so they can be very expensive, but sample collection is easier for than blood or DNA. Sequencing, biomathematics, and immunological studies take time, effort, and money.

Ms. Harris noted that the collaboration goes across three continents and wanted to know if the collaborations were all with academic institutions and based on relationships he and his colleagues have with them. Dr. Baranzini indicated that they were teaming up with people they thought were the best at the different facilities around the world.

Ms. Harris asked if there was a life sciences or medical facility in San Francisco where this project could be financed through philanthropic organizations. Dr. Baranzini indicated that UCSF has an office of development through the California Institute for Quantitative Biosciences (QB3). California has an incubator for startups and they can link people to entrepreneurs and philanthropists. Each department also has an office of philanthropy. Ms. Harris indicated that there is a lot of funding available, so scientists should be able to get enough money to do this kind of research because the Veterans need this. Dr. Baranzini agreed. Dr. Hauser also agreed and noted that discovery science is very difficult to get funded in peer-review.

With that, Dr. Hauser thanked Dr. Baranzini and introduced the next speaker, Dr. Lorene Nelson. She is an Associate Professor at Stanford University in the Division of Epidemiology, Department of Health Research and Policy, and Associate Director of the Center for Population Health Studies.

Research with Large Administrative Health Care Databases: Challenges and Strategies
Dr. Lorene Nelson

Dr. Nelson discussed the challenges and some strategies for using large administrative health databases to conduct epidemiology research. The main effort is to study the adverse health outcomes that accompany service in the Gulf. Dr. Nelson served on the IOM committee that was asked to focus on neurological outcomes associated with the 1990-1991 Gulf War and post-9/11 wars.

That IOM committee had been asked to determine how to conduct an epidemiology study of the incidence, prevalence, and risk of developing MS and other neurologic diseases, Parkinson's disease, brain cancers, migraines, and "central nervous system abnormalities that are difficult to precisely diagnose." This subject is difficult to study with administrative data and ICD-9 codes. The report came out in December 2015, and Dr. Barbara Vickrey briefed the RAC in April 2016.

As an overview of her presentation, Dr. Nelson outlined the three main topics she planned to cover: (1) a review of sources of bias by study type (selection bias and misclassification), (2) the use secondary data sources to determine health outcomes (utilization data, electronic health records, death certificates), and (3) her own work in estimating the national prevalence of multiple sclerosis for the MS Society. She planned to explain how these topics could apply to Gulf War Veterans.

Dr. Nelson indicated that approximately 600,000 Gulf War Veterans deployed in 1990-1991. Some were highly exposed to oil well fires, nerve gas, and some were not but then they were exposed to other things in the region. Approximately half of a cohort of 750,000 were not deployed to the Gulf and formed the control group, stratified and oversampled for females and racial and ethnic diversity. She went on to describe the kinds of designs that can be used when trying to find health outcomes in these big cohorts, especially since 25 years had elapsed since the exposures of interest.

One approach is to use surveys, as the Office of Public Health began in the early 1990s when they selected 15,000 deployed and 15,000 GW-era Veterans. They followed-up in 2003-2005 and 2012-2015 by trying to recruit the same 15,000 people in each group. In 1995, the response rate from Deployed Gulf War Veterans was 70% and was 64% for the controls. In that survey the prevalence of multisymptom illness was 37% for deployed versus 12% among GW era Veterans. In the 2003-2005 follow-up, response rates were only 41% and 26%. In an article published this year regarding the 2012-2015 survey, response rates were 57% and 43%, and the prevalence of GWI was 44% in deployed Veterans and 20% in the era Veterans.

Another way to design a study for these large cohorts is "data linkages." An example is the mortality data follow-up of this cohort through 2004 and again through2011. Gulf War Veterans had a higher rate of deaths from motor vehicle accidents than era Veterans.

There have been studies using VA health care data over the time frame of 2002-2013. Dr. Wallin did a very rigorous study of MS and Gulf War Veterans in which he saw a lower incidence of MS in deployed Veterans, a 30% reduction compared to controls in 1990-2007. The other thing that can be done is to link these cases to the Cancer Registry data. When this was done through 2006, the was an increased incidence of lung cancer among those who served in the Gulf War, but smoking and other risk factors were not controlled.

The biases that are important are the following: (1) Selection bias, which can be as simple as selective non-participation by individuals, (2) Volunteer bias, in which the individuals with the exposure of interest are more likely to participate, (3) Methodologic bias, in which VA data is biased because not everybody has the same eligibility or coverage at VA or there is selective attrition by cohort. Surveys allow very detailed data to be collected; that is not possible with health care data linkages.

Dr. Nelson wanted to focus on measurement error and misclassifications. With surveys, recall bias can be a factor because those with exposures are more likely to recall specific incidents. Disease misclassification can occur in any study. Surveys can be particularly good for assessing symptoms because those are not picked up by ICD-9 codes in health care data, and misclassification can occur using ICD-9 codes to infer that a disease is present. These potential biases are less confounding in surveys and disease registries where data on confounders can be collected.

In trying to study symptomatology, the best way to do it is with surveys. For diseases like MS, PD, ALS, and cancer the information from surveys is not typically as good. Mortality data work well for fatal diseases like ALS and brain tumors. VA data linkages might be better for diseases like MS, PD, and ALS, but it is less likely that Gulf War illness can be evaluated this way. Disease registries can ascertain outcomes in the two big Gulf War cohorts, but you have to have a national registry that is fairly complete.

Right now we only have that for cancer and possibly the recent national ALS registry sponsored by CDC.

"Secondary Data Sources" are those data that have not been collected specifically for research. The three main kinds of secondary data are (1) administrative healthcare data, (2) electronic health care data, and (3) death certificates, and they can be linked to the original cohort members.

Death certificates can be good for conditions that end in fatalities, but coding is very critical in those studies and could introduce error. Many chronic conditions like MS and ALS could be misclassified. In terms of selection bias, there would not be differences in errors in death certificates for deployed and non-deployed Veterans so using death certificates is probably a good method for following the Gulf War group in an unbiased way.

Dr. Nelson indicated that administrative health care claims data is where most the work with large databases has been done. These data are collected for payment of clinical services, hospital admissions, outpatient visits, laboratory tests, diagnoses, procedures, and medications. These are reasonably accurate data; however, the ICD-9 codes are not always accurate, and lab results are frequently not available.

To use VA health care data for the two big cohorts, it is important to remember that 46% of the deployed and 36% of the non-deployed use VA health care. Electronic health records have not been widely used for big epidemiology studies because there is a challenge extracting all the rich clinical information.

Dr. Nelson and Dr. Wallin are involved with estimating the prevalence of MS as part of the MS society's National MS Prevalence Working Group. Other than the SEER (Surveillance, Epidemiology, and End Results) cancer registry and now the ALS registry, there are no nationwide registries of chronic conditions. Much of what we know about MS comes from small cohorts.

The biggest challenge in trying to estimate the national prevalence of MS is that the US health care system is somewhat fragmented. Medicare covers healthcare for 93 to 95% of the people over 65, so that would be an easy target. In 2007, for people under 65, 62% of people were insured through their employer, 3% by Medicare, 11% by Medicaid, 6% were self-pay, and 17% were uninsured. The Affordable Care Act should change the percentage for uninsured. In the IOM committee, Dr. Nelson and the others were asked how best to access the prevalence data. Perhaps the commercial claims databases (such as Optum, Truven, IMS Health) that give access to the claims handled by United Health, Blue Shield, and other big groups would be useful. Medicare, Medicaid, and possibly VHA data are theoretically available for assessing the prevalence of MS; however, it is difficult to do so for any uninsured and self-pay individuals.

There can be a problem of using ICD-9 codes alone to determine whether there is a diagnosis of a neurological disease or not. The gold standard is the medical record, and it is necessary to develop claims data algorithms for figuring out which codes will give the best representation of disease diagnosis. Previous studies showed that their algorithm gave 87% sensitivity in the group that truly had MS. The specificity (those who truly do not have MS) for the algorithm was 83%. The positive predictive value (the percent of the time the diagnosis is correct) was approximately 98% in the example.

The quality of these algorithms would vary by disease type. For example, for Parkinson's disease there was a lower sensitivity of 70-73% using claims data. The specificity of 80-85% is in the same range as MS; the positive predictive value was much lower, 80-85%.

For Gulf War Veterans, the IOM committee asked for follow-up data covered by VHA between 2012-2013. Each of the conditions had a single ICD-9 code that can give false positives. There was a higher occurrence of migraines in deployed versus non-deployed Gulf War Veterans. For MS and Parkinson's disease, there was no increase in deployed Veterans in data back to 2013. These results are just for the two big cohorts, so it does not necessarily reflect the smaller studies done in different regions of the country.

In conclusion, Dr. Nelson said that Gulf War research is challenging. Possible future work involves continuing to follow the GW cohorts. Other approaches would be to use more sensitive algorithms than single ICD-9 codes, or to consider the subset (from 1995) that had survey data with a higher percent participation rates and link that to later VHA data or to cancer registry data. Perhaps for the future, it would be possible to investigate electronic health records to reduce the misclassification that you get in claims data, and possibly analyzing the data in VINCI.

Mr. Bunker commented that one problem with the VA data is that the non-deployed or those deployed later make up approximately 20% of the cohort. Some were deployed to the Gulf after the cut-off date and were there during the Khamisiyah detonations. So that has to be considered when discussing brain cancer.

Mr. Nast reminded the Committee that there were many troops who are prepared for overseas movement, even though they were never deployed. They took the vaccines and did other preparations, so this could be a confounder.

Dr. Nelson asked Mr. Bunker what the prospects are of going back now and fixing the deployment data in those large cohorts. Mr. Bunker indicated that Dr. Erin Dursa at VA looked at the data and came up with the 20% then mentioned it in one of our biweekly teleconferences. It can be done. Mr. Bunker continued and said that VA electronic medical records only go back to 2001. All the medical records from the 1990s, including who went to the Gulf War clinics, have never been reviewed. Over 100,000 Gulf War Veterans went in to have things done in the Gulf War clinics or the exams. His opinion

is that VA is unlikely to spend the money necessary to digitize these old medical records.

Dr. Klimas noted that Veterans in general have more exposures than civilians and asked if there was a civilian control that would be better, but Dr. Nelson was not aware of one. Dr. Klimas noted that Gulf War Veterans constitute a large group, but only 30 to 40% are in the sick group and it is difficult to determine who they are. In the first survey, 10% of the non-deployed reported symptoms of Gulf War illness. If 20% of those were actually eventually deployed, that would be another problem. This is higher than the chronic fatigue syndrome's civilian background which is around 1 or 2%.

Dr. Wallin asked what Dr. Nelson thought about using Medicare-link with these conditions. At 25 years after the first Gulf War, it seemed like it would be useful to know what happens to these people as they approach Medicare age. Dr. Nelson noted that they were 27-28 years old in 1990-1991, so 25 years later, they are 53 or so, so they are still a few years from entering Medicare eligibility. It's still a pretty young group, though, so Medicare would be important later.

Dr. Wallin commented that it might be necessary to use existing databases and cancer registries instead of Medicare data. Using the Gulf War data, even for the well-defined diseases, it is very difficult to define an algorithm.

Dr. Hauser referred to the UC database for two comments. It is possible to improve the MS data extraction reliability by "smart searching," which includes therapies in the case of MS. If you "smart search" the text, you can get correlations that are useful. The other approach that could be very helpful is to test the extraction accuracy against the well-curated (smaller) research databases. If you have 500 patients in a study you can capture those patients in the electronic medical record and see how well that corresponds to your phenotype. Dr. Nelson agreed with those comments, and suggested that natural language processing could be used to obtain some of the other information.

Dr. Rauch noted that the concerns about misclassified data are unnecessary unless one hypothesizes that the 20% later deployed were more susceptible. He suggested that you could reassign them as deployed and it wouldn't change those results. It also raised the question of whether their health status was a result of their Gulf War experience. It might be a concern if the study were underpowered, but that does not seem to be a factor in this case.

Dr. Tanner noted that there were additional problems that have to do with diagnostic misclassification as well, and if one chooses to use the least sensitive algorithm and, therefore, have the greatest amount of diagnostic misclassification. There is also another source of potential bias - the healthy soldier effect. The non-deployed may have had some medical reason for not being deployed. There is a lot of uncertainty in this particular cohort classification. Dr. Nelson's point is well taken mathematically, but there are lots of limitations. Dr. Nelson indicated that the ICD-9 code introduces a lot of

problems. If it were possible to use more sensitive case-defining algorithms, that would allow you to do better. Mr. Bunker commented on Dr. Tanner's point about the healthy warrior effect. Everyone received good physicals before deployment. If someone did not do very well on theirs, then they would not be deployed. Active-duty personnel would be processed out of the service; Guard and Reserve personnel may have been treated the same way. All those people would be on the non-deployed list because of their health conditions; healthy people were more likely to be deployed.

Dr. Ashford commented that there is a Gulf War Registry run by the Office of Public Health. There were some really good data collected in the Registry, and he would like to see the Registry put into good shape so it could be used for recruiting patients for research. Dr. Nelson wanted to make it clear that her comments were about large national registries for cancer and neurologic diseases, not Gulf War. Mr. Bunker indicated that some places, like his VA, do a bad job with the Registry examinations, and at Ron Brown's, they do not do Registry examinations at all.

Dr. Hauser thanked Dr. Nelson and announced that Public Comments would begin after a ten-minute break.

Public Comment

Ms. Denise Nichols wanted to mention first that she enjoyed the research presentations during the day. She was concerned that the RAC meeting had apparently not been publicized enough because there were very few Veterans present. She also suggested that RAC meetings should be held at different venues, especially in places like Minneapolis, Miami, Houston, Atlanta, and Birmingham AL. She asked when and where the next meeting would be held. Dr. Klimas mentioned that the NIH has the same problem with their chronic fatigue syndrome meetings, so they try to have "mini-meetings" with patients to encourage patients to attend. Denise suggested that there could be Veterans' meetings in Washington DC before RAC meetings. She also encouraged VA to reach out the Veterans who are medical professionals and invite them to meetings.

Mr. Dean Lundholm, a disabled Gulf War Veteran expressed frustration with his treatment and diagnosis. In November he had aa terrible cold and sinus infection. When he was treated with antibiotics, the infection cleared up. When he stopped taking antibiotics, the infection returned. He received diagnoses of optic neuritis, infection in the brain and allergies. He had endoscopic sinus surgery. He was frustrated because he felt like his only option was to wait until his providers figured out what was wrong with him. On another topic, he indicated that he cannot afford to travel to Florida or Texas, or anywhere else, to participate in studies. He would be happy to participate from California and send blood or CSF specimens.

Ms. Nichols indicated that she had tried to coordinate with VA hospitals to share clinical laboratory services for research patients. She would also like to see follow-up after WRIISC visits because the local PCPs do not use WRIISC suggestions. She also

wanted to make the Committee aware of additional health issues in the Gulf War cohort: dental problems, skin rashes, eye problems, cardiovascular problems, renal and liver problems, and viral problems.

Ms. Kim Adams was also disappointed that more Veterans did not participate. She indicated that a lot of VAMCs are not conducting Gulf War Registry Examinations. VA needs to find a better way to encourage Veterans to participate.

Dr. Giulio Pasinetti from Mt Sinai School of Medicine commented on the microbiome lecture. He indicated that we are just at the beginning of new, exciting science and that we need to understand the interrelationship between the brain and gut. This will help to cure diseases and deliver new therapeutic drugs.

Dr. Fiona Crawford said that we need to fund Veterans to travel to research sites, they need to sign consent forms, and we need to draw blood, etc. Also import is to process the blood or other specimens in ways that will be useful to researchers. Her facility is having an "open house" around Veterans Day to let Veterans and the rest of the public learn about the Gulf War, TBI, and PTSD research that is going on.

Ms. Nichols indicated that approximately 480 Gulf War Veterans attended a Memorial Day parade in Washington DC. She wondered what could be done with the Gulf War Registry. Does VA know how many people are in the Registry? Should they all be re-surveyed?

Dr. Hauser closed the day's meeting by suggesting that these topics should be part of Committee discussions as we move forward.

DAY 2

Call to Order and Announcements

Dr. Hauser welcomed everyone and opened the meeting by briefly reviewing the day's agenda. He mentioned that the Committee Discussion would include draft recommendations and that the meeting would end at 1:00pm.

Dr. Hauser introduced Dr. Adam Gazzaley, Professor of Neurology and Physiology at UCSF. He is a neurologist and a systems neuroscientist who studies the ways that networks of nerve cells work and produce behaviors. His work with modulation and rehabilitation of cognitive issues has led to novel interactions between academia and the world of technology.

Technology meets Neuroscience - A Vision of the Future of Brain Health
Dr. Adam Gazzaley

Dr. Gazzaley began by stating that technology will be increasingly involved with neuroscience in the future, in fact, the immediate future. So his focus was on where we can go. Among his other activities, he was involved with PTSD and TBI studies at the San Francisco VAMC, and he felt that the principles underlying those studies could be useful to Gulf War Veterans.

Dr. Gazzaley spoke of cognition is the broadest sense when he said that there is a significant challenge in improving cognition in healthy as well as ill individuals. There are fundamental problems with the current system of assessing and treating patients with neurological problems: (1) Very poor assessments are used. The newest technology does not translate into the clinical practice of neuroscience. (2) Patients are treated even though diagnoses are not perfect. Pharmaceuticals have been used for many years, and eventually the appropriate drugs are found for a patient. (3) Treatments are not personalized. Many physicians prescribe a few drugs that work for most patients (4) An open loop system has minimal feedback from the patients. The feedback needs to be more than dynamic than waiting until the patient's next visit.

Dr. Gazzaley's plan was to create a targeted, personalized, multimodal, and closed loop system to study and improve brain function. His approach was to use familiar consumer technologies like virtual reality, augmented reality, wearable physiological devices, 3-D video game engines, artificial intelligence algorithms, and motion capture to create better tools to understand and improve brain functioning.

By creating experiences Dr. Gazzaley hoped that they could improve brain plasticity. modern tech enhance cognition, refine behavior, and improve the mind. He also wanted to create a closed loop system in which data could be used to update and refine an intervention.

Since many people play interactive video games, Dr. Gazzaley wondered if he and his team could they create a game that required multitasking to improve and an aging person's ability to multitask enter (similar brain network - would there be improvements in other effects like attention and working memory)

They designed "Neuroracer," a video game with no violent content in which a player drives a car and responds to road signs. As the game proceeds, it gets harder, and to get from one level to another, the player has to improve in both tasks. They conducted three years of studies testing it as a behavioral and neural diagnostic tool, with the hopes that they could modify it to be an intervention to improve brain function.

They tested 20-year-olds and 80-year-olds. Each group started by responding to the "road signs," and then the "driving" task was added. With the second task added, there was a 27% decrement in the ability of the 20-year-olds to deal with the road signs. The performance of the 80-year-olds was much worse. They could monitor the players'

brain function using EEG or MRI to monitor brain function. EEG topography plot were generated during the game play.

The older adults were not engaging the prefrontal cortex as well. This fact was already known, but Dr. Gazzaley could see the effect in real time.

The older participants (60-80-year-olds) took the game for home training for one month. They played one hour per day, three days per week for four weeks in a closed loop fashion. There was a significant improvement in their ability to multitask, even exceeding the 20-year-olds. Even six months later the ability to multitask was still improved. Other cognitive skills improved as well, thus confirming their hypothesis that you can demonstrate transfer and sustainability; the same game without multitasking showed no improvement and no transfer of benefits.

Their conclusion was that the "active ingredient" in Neuroracer was the multitasking, and this was published in Nature in 2013. Neuroracer is a prototype of a game; it was not amenable to large scale tests. Dr. Gazzaley filed a patent for the methodology, formed a company called Akili Interactive Labs, and licensed the UCSF patent to them. Akili has already made a much better game called "Evo" which uses an iPad and has other improvements. Akili is conducting multiple clinical trials involving PTSD, TBI, autism, Alzheimer's disease, depression, multiple sclerosis, anxiety, and addiction. All those populations have cognitive control deficits. The FDA approved Evo as a treatment for ADHD, and a double-blind randomized-controlled trial is going on now at eight sites on the East Coast. Games could be available by the next year.

More recently, Dr. Gazzaley has set up a new laboratory called "Neuroscape Lab." They will do additional research to develop and validate hypotheses. Just outside the lab, they can do MRI, phlebotomy, EEG, and stress metrics. They record everything possible on study participants (eye movements, body movements, autonomic responses, brain activity, and behavioral performance) to understand the changes that occur in the entire human system. Dr. Gazzaley wants to develop games in which people play with their entire bodies, not just with their eyes and fingers.

Examples of the games they have developed are Meditrain, Rhythmicity, Virtual Attention, and Body-Brain Trainer. Meditrain is a videogame on an iPad that can teach people to meditate and control internal distractions. It is also known that meditation can help cognition, stress, and mood. Rhythmicity was developed with Mickey Hart (percussionist from The Grateful Dead) and other musicians. If a person can become more rhythmic, there is an improvement in the rhythm of the brain and cognitive performance. Virtual attention uses a virtual world to teach patients to focus their attention and broaden the distribution of their attention in both space and time. This is especially useful when driving. Body-Brain Trainer (BBT) challenges both cognitive and physical fitness at the same time by adding a motion capture system to the cognitive measures. And both systems are in closed loops to provide feedback. Players wear a heart rate monitor, and before starting the game, Dr. Gazzaley's team measures the

VO2 max and determine each player's anaerobic threshold. For Dr. Gazzaley, the optimum heart rate was between 120 and 140, and the game is designed to keep the player's heart rate in the desired range. If the heart rate is below the goal, the game detects this and increases the movements required by the player; conversely, if the heart rate is too high, the necessary movements are reduced. And this physical closed loop operates while the cognitive challenges are being done. Their hypothesis is that a player gets a better experience if the game combines physical and cognitive challenges.

To try to understand the mechanisms involved, Dr. Gazzaley's team is studying MRI functional and structural changes, stress monitoring, cognitive testing, blood work looking for inflammatory markers, hormones , telomerase activity, i.e., anything that can change. They have also learned how to conduct placebo-controlled behavioral trials. They want to look at how different games can interact - sort of a "Neuro-CrossFit" approach, so video games are just the beginning as they put other tools of neuroscience to use.

Dr. Gazzaley has developed the "Glass Brain." They have taken structural MRI data and overlayed 64-channel EEG data, all collected while game-playing. He hopes to figure out how brain areas are communicating with each other during an interactive activity like game-playing. The Glass Brain is a data visualization tool, a proof of concept. Now they have to use it both as a diagnostic tool and to close the loop for their therapies.

Currently, a patient with a neurological problem is likely to get drug which can activate the brain in a diffuse manner. While it is reasonable to treat patients with pharmaceuticals, over the next five years it should be possible to reduce the dose levels of drugs by also using an Adaptive Cognitive Evaluation (ACE) app which uses closed loops to rapidly sample the whole set of cognitive control abilities.

Better assessment can give the patient a tailor-made package of games that target the neural networks that need re-training. A patient could wear a cap at home to record brain activity and feed it into the game engine. Then the game would be responding to the way the patient processes information in general, not just the way he/she plays the actual game. With that feedback, the game engine can determine if there is a visual processing difficulty, attention deficit, or any of a number of problems.

Dr. Gazzaley envisions an external transcranial stimulator that can accelerate the learning curve to treat, for example, patients with TBI. Feedback can direct the engine at the brain processes that need to be improved. Perhaps this approach can be combined with low dose drugs to get a better effect than drugs alone. Over the next ten years there should be results from clinical trials which have already started or will start soon. These concepts might help healthy brains as well, for example, as wellness tools for the elderly or as educational tools.

Dr. Hauser commented that these technologies have a lot of exciting possibilities for helping our Gulf War Veterans.

Dr. Klimas stated that GWI has neural inflammation and neurodegeneration. Since Dr. Gazzaley's design helps neural plasticity, she wondered how he and his team deal with inflammation. Dr. Gazzaley said that his approach is a combination therapy. The four largest investors in his company were pharmaceutical companies. It is not known how neural inflammation and plasticity interact unfortunately. The details on how the games can change neural inflammation are not known, either, but they seem to increase the selectivity of drugs that help neural inflammation. If the brain needs a particular drug, then the brain creates its own selectivity. So, selective activation of the brain can change the specificity of drugs.

Dr. Wallin asked how the video games translate into real world problems like finding your car in the parking lot. Dr. Gazzaley indicated that they do not know that yet. His group looked for a signal, and they saw changes and improvements, but there is more work to be done.

Dr. Wallin suggested that there need to be much bigger clinical trials. Dr. Gazzaley reminded everyone that his studies are on healthy older adults who have the problems of aging, so adjusting to address the problems affecting ill people may be more difficult.

Dr. Hunt asked how Dr. Gazzaley could envision his approach being applied to go ill Gulf War Veterans, and secondly to Veterans with PTSD. Dr. Gazzaley saw the potential complication of PTSD on top of other neurotoxins in Gulf War Veterans. He already has great interest from Veterans for the PTSD trial. Veterans are a very important population to consider using this technology therapy on. These tools require a lot of participant interest and motivation, and Veterans are very motivated. There is no violent content, and that makes it potentially useful for Veterans. It takes about two years to create a game for a particular population. The first step would be to identify their problem and come up with a plan for assessing that problem. Then they would start with an existing game to see if they could modify it.

Dr. Philbert asked about the contribution of the dopamine-serotonin axis and whether it (rather than re-wiring the prefrontal cortex) might be responsible for the cognitive improvements. Dr. Gazzaley said that their data show that prefrontal cortex function is improving. He indicated that he believes that the dopamine system is involved; the brain's systems are constantly interacting. They are using more sophisticated neural metrics, stress, and inflammatory markers in the studies that they are doing now. These will help to understand the mechanisms. Dr. Gazzaley thinks that the games improve the efficiency of the prefrontal networks to engage during a challenge and that this might be the reason that it transfers to other cognitive operations.

Dr. Philbert asked if it was possible to overlay the game onto three dimensions. Dr. Gazzaley indicated that they are using virtual reality and developing new games. He suggested, for example, that an autistic child could learn social skills on a virtual platform before having to deal with people. Some games are augmented reality, which is an overlay onto the real world; three companies are working on augmented reality.

Also the games developed thus far are for one person alone interacting with the game. In the future, multiple players playing the same game will bring a whole different social aspect to the process.

Dr. Klimas commented that if Dr. Gazzaley can keep patients under their aerobic threshold, they are in a safe place. If the patients go over that, it can cause a problem, so that is very important for this Gulf War population. She liked the idea of combining physical feedback with cognitive retraining because they can have a problem with overdoing it. Combining cognitive and physical training while they are under the aerobic threshold can possibly move their aerobic thresholds. She asked if he had any ideas for this work applied to GWI. Dr. Gazzaley commented that he could not have said that better. He indicated that it would be easy to set certain parameters to do exactly what she suggested.

Dr. Hauser requested a five-minute break. After fifteen minutes, Dr. Hauser introduced Dr. Wes Ashford. Dr. Ashford is Clinical Professor of Psychiatry and Behavioral Science at Stanford and Director of the War Related Illness and Injury Center at VA Palo Alto. After Dr. Ashford's talk, a roundtable discussion with all three WRIISC Directors was scheduled.

WRIISC: A Resource for Veterans, Providers, Researchers
J. Wesson Ashford

Dr. Ashford had presented to the RAC before, but wanted to indicate how the WRIISC has tried to provide a resource for Veterans, clinicians, and researchers. The WRIISC was created following Public Law105-368 in 1998 and an IOM report. The first two WRIISCs were in New Jersey and Washington, DC, then in 2007 Palo Alto was added. The WRIISC was under the VA Office of Public Health, and has now been moved into Patient Care Services under Dr. Lauren Erickson. The main mission is to see Veterans clinically who have been referred to their program. This requires an "intra-facility consult" (IFC), and a provider needs to go into CPRS, look under "Consults," then "WRIISC."

Most of their consultations are post-deployment Veterans, some of the most difficult patients to diagnose. Half of their referrals travel to the WRIISC sites; half are electronic consults. They conduct a complete evaluation, including exposures, on patients. The WRIISC has educational webinars, a newsletter on a regular basis, and an annual report. During the last five years, they have been working on getting better data overall and combining the data from all three locations. The WRIISCs had 2500 patient interactions in 2015, over 1000 of which were in complementary and integrative medicine. Of the patients referred to the WRIISC, 98% said that they were taken seriously by WRIISC providers and they received good treatments.

Last year, the WRIISC presented 28 webinars with 6500 attendees, and they provided

training for Veterans. WRIISCs have a website (www.warrelatedillness.va.gov), and publish a newsletter three times a year. They have approximately $25M in funding across the three sites and produced 54 publications last year.

Dr. Ashford indicated that the problem they usually have at the WRIISC is that the Veterans come to see them and tell them what is wrong because many of the doctors in the field have not had enough experience to help the Veterans. So, the doctors have to understand the basic issues facing Gulf War Veterans.

Of the 820 consults (by era) at the WRIISC last year, 40% came from Veterans of Operations Desert Shield/ Desert Storm, and they define this group as having served in theater from August 1990 to June1991. Since the "Gulf War" is still going on, it is important to focus on a specific group. He said that Desert Storm was not over until 1992, according to some reports.

One of the things they ask at the WRIISC is for Veterans to list their top three symptoms. Pain is the number one problem; nearly all complain of pain. Number two is mental health problems (PTSD, and secondary issues of depression and sleep, with a few cognitive complaints). They also see GI problems, headaches, chronic fatigue, and respiratory problems. There are not as many cardiac problems in Gulf War Veterans as in Vietnam Veterans.

For background, the invasion of Kuwait occurred on August 2, 1990, and our troops began to arrive on August 7. One Veteran said that he was there in July in anticipation of the invasion. The air war started on January 16, 1991, the ground war started on February 24 and ended on February 28. The Khamisiyah detonation occurred on March 10, 1991.

Mr. Bunker commented that the first Khamisiyah detonation was on March 4, the second large one on March 10, and the last large detonation was on April 2 or 4, according to the DoD website. Dr. Ashford reminded everyone that the point of mentioning various dates is so he can get a timeline for each Veteran who comes to the WRIISC. Mr. Nast said that his unit, the Second Brigade (Blackjack Brigade) of the First Cavalry Division attacked around Valentine's Day, 1991. It was an initial feint attack up the Wadi Al-Batin, and there were casualties from direct enemy fire. Dr. Ashford commented that medical students and new doctors in VA have no idea of what happened and what people were exposed to. This is important information for VA to have; all these personal details should be in Registry exams. Mr. Bunker said that Mr. Nast was talking about raids that started as early as February 1. He added that DoD's Gulflink website will show the last large explosion in April, 1991.

Dr. Ashford commented that the exact dates are not as important as figuring out what people were exposed to, so it is important to know when people were in the Gulf and where they were. It is easier to show Veterans a map to find out where they were during different periods of the Gulf War. Some were at the front; others behind the lines repairing tanks, etc. The living conditions were terrible – housed in crowded tents,

temperatures that were very hot or very cold, eating MREs. The first groups deployed to the region ate local food, and many became ill. Mr. Bunker said that the bottled water originally had sugar and fecal matter in it. He has a DoD training video that indicated the sabotage.

Dr. Ashford continued. There were issues with sanitation, sand flies, insecticides, and hazardous materials. Troops were exposed to pyridostigmine bromide (PB) pills, but not all troops took the pills. There were 293 deaths in theater, 148 in combat (35 friendly fire) and 145 non-combat deaths. There were 20,000-35,000 Iraqi killed, and another 75,000 injured. Among Kuwaiti civilians, 1000 were killed and 600 were missing. Approximately 3500 Iraqi civilians were killed.

Exposures included weapons, the local environment, preventative treatments, and occupational agents (diesel, kerosene, gasoline, vaccinations). Louise Mahoney said there were cell phones in use for the first time; they had their own local satellite. Mr. Bunker said that the large microwave radar towers for artillery should be added to the occupational hazards list.

Chemical weapons exposures were expected, so Service members had to wear MOPP suits. There were anecdotal reports of exposures to chemical agents, but no acute cases of sarin poisoning that Dr. Ashford has seen. One Veteran told Dr. Ashford that he carried a sarin canister out of country and had it on his back porch. DoD notified 100,000 Veterans that they may have been exposed to chemical agents, but there are no specific tests.

The RAC has supported the notion that anti-cholinesterase agents, like sarin, PB, pesticides, and others, are responsible for GWI. Permethrin is not an anti-cholinesterase agent, but it acts on certain sodium channels that interact with anti-cholinesterase agents. Additionally, a lot of Veterans are concerned about depleted uranium (DU).

Dr. Young said he was in country as a flight surgeon. He and his colleagues had been training against a "Soviet threat" when thinking about NBC warfare. They had not been training for exposure to biological or chemical weapons in the way that the Iraqis might have used them because nobody thought that anyone would be crazy enough to do so. Dr. Young was concerned that he might have to take care of people in the field who had been exposed to acute levels, high levels, of chemicals or biologicals. There was a lack of sophistication of what was done in the field, but you have to be put into the context of the training at the time.

Dr. Ashford had worked with Dr. James Stutts who was deployed. The first time Dr. Stutts heard the chemical weapon alarm go off, he pulled out his physostigmine needle and gave himself an injection so he would be prepared to treat others. There was some concern about how much sarin was actually there. "60 Minutes" did an article on the Syrian government using chemical weapons against its own people.

Dr. Rausch asked two questions: (1) Did the troops on the ground know that the combat-related versus non-combat-related deaths were about 50-50? (2) How did this ratio compare with various wars over the years? Is this a remarkable statistic or not? He asked because there is a very different neurobiological response between an unknown threat and a specific threat. Dr. Young gave examples of non-combat deaths - helicopter crews caught in sandstorms, accidental gunshot wounds, austere and fairly hostile environment, etc. Dr. Ashford indicated that there were fewer deaths among soldiers than there would have been in a comparable group that stayed at home; he wondered if this was the healthy warrior effect. Motor vehicle accidents were the main cause of death in the non-deployed. All these issues are important when trying to manage healthcare for patients.

Dr. Ashford added that there were fears about DU, too. There were burn pit exposures and respiratory problems. Over 700 oil wells were on fire. Some of the troops who are in the West and Central part were not in the oil fire plumes, but Navy personnel in the Gulf were under the plume. The respiratory problems are partly due to the cilia not beating to clear the lungs; nicotine can cause the cilia to beat less than normal, and some people started smoking during the Gulf War deployment . There is a Registry for people who have been exposed to airborne hazards (burn pits).

Many troops also had chronic fatigue, skin rashes, and headaches. Deployed Gulf War Veterans reported twice as many symptoms as non-deployed Veterans. In a recent article by Dr. Erin Dursa and co-workers, 44% of the people in the longitudinal study have the same conditions they had been 1990.

Dr. Ashford indicated that the Institute of Medicine (IOM) had made a number of recommendations regarding Gulf War research. The IOM recommended the use of the term Gulf War illness (GWI), and a VA decision is pending. VA does use the two definitions recommended by IOM - the CDC and Kansas definitions. There is not a WRIISC definition, but they report the symptoms that a Veteran has. Chronic multisymptom illness is observed in other groups, and Gulf War illness is under that umbrella. Unfortunately, there are no validated tests for GWI/CMI yet.

Dr. Ashford summarized findings from ill Gulf War Veterans and remarked again that there are no validated diagnostic tests. He also listed some possible explanations related to exposure to anti-cholinesterase agents: (1) Idiopathic small fiber neuropathy, (2) Autonomic nervous system disruption, and (3) Tardive Sympathetic Dysautonomia (TSD, a hypothesis of Dr. Ashford's). He also listed treatment strategies: (1) Identify the GWI symptoms in the patient, (2) Use a team approach to provide comprehensive care (personalized, patient-centered care; PD-PACT; with the WRIISC program as a model). He emphasized that there is no single therapy, but they can treat the symptoms. Once the symptoms are identified, patients can be referred to the proper clinics and specialists.

Dr. Ashford indicated that one of the most difficult tasks they face is recruiting Veterans into their studies. Clinically, they are able to get the Veterans in to get an idea of their

medical issues. Then research projects can be designed around the Veterans' problems and concerns. Collaborating with other investigators is one way to increase the number of well-trained providers in the field. They are currently recruiting for a pain project and a complementary and alternative medicine trial.

Dr. Ashford closed by posing the question, "How can the RAC help the WRIISC?" He said that the RAC could support the Post-Deployment Health Services and WRIISC initiative to develop a VHA directive for PDHS which included making WRIISC a distinct service. The RAC could help to ensure that the WRIISC has adequate personnel and funding for the clinical, educational, and research mission. Finally, the RAC could consider supporting the idea that the WRIISC should be designated as a post-deployment champion.

Dr. Hauser thanked Dr. Ashford and invited the other WRIISC Directors, Dr. Helmer and Dr. Reinhard, to join Dr. Ashford at the table for a discussion with the Committee.

Roundtable Discussion on Integrating Research and Care
WRIISC Directors

Dr. Klimas asked if the transfer to PCS will change WRIISC's research charge. Dr. Helmer responded that it would not. In some ways, WRIISC was the most logical part of OPH to go to PCS because the WRIISC sees patients. Then it is possible to design a research program around the patient care. Dr. Klimas followed-up by asking how the WRIISC can promote a collaborative spirit in the whole VA. Dr. Helmer said that there are lots of examples where WRIISC is collaborated on numerous projects. WRIISC is generally open to collaborating and leverage their resources with other SMEs.

Dr. Klimas commented that the Committee often talks about barriers to getting research done and pointed out that access to subjects is a real problem. In trying to recruit subjects, collaborating is one way to get subjects into a research project. She asked if there was anything that the WRIISCs can do to help the investigators get access to subjects. Dr. Helmer said that they would like to see a centralization list of the Veterans who should be included in this group – not just for research, but also for clinical management. From available data, it is not always clear who deployed and who did not. The quality of the data supplied by DOD is quite variable. He would like to see the Gulf War Registry data modernized and made more useful. Part of their success at the WRIISC has been that they have their own patients, and they can approach them to participate. However, they do not necessarily have access to the larger group any more so than other researchers would; therefore, the WRIISC also relies on many different kinds of recruiting efforts. Dr. Ashford indicated that the WRIISC has to be able to recruit its own participants. Registry data can give information about Veterans local to their facility, but the data are not always accurate. It needs to be updated; a concerted effort for recruiting would be very useful.

Mr. Bunker said that the Registry had over 100,000 names in it in 1999, and VA was supposed to be using that to send out the Gulf War newsletter. He also indicated that a

lot of Veterans are trying to get referred to the WRIISC. He was concerned about their capacity; when he went to the Washington, DC, WRIISC for a week-long neurological workup, he found that there were only two beds. He has also heard from Veterans in the New Jersey area who get tired of being called in because they are healthy Veterans.

Dr. Helmer acknowledged that they had seen an increase in the number of referrals to the WRIISC in the last three years. They have expanded the scope of the clinical activities to include "e-consults." They assess the consults as they come to the specialty services, and then they do medical records reviews and respond, if possible. So WRIISC has not been able to increase capacity for in-person consultations. Two people per week is the maximum at each location, so that is about 300 per year. The remaining 700 are telephonic or electronic consults, and that is their limit with the resources they have. There had been some discussion about the availability of deployment-related specialty care in VA medical centers in general so people would not have to travel. Such a plan would be predicated on the competency, knowledge, and skills being available at every VA facility.

Dr. VanLeeuwen announced that Dr. Peter Rumm from PDHS had joined the meeting by telephone. Dr. Helmer introduced Dr. Rumm as the Director of the Pre-9/11 Era Environmental Health Programs in Post-Deployment Health Services. He had been with PDHS for approximately five months and has the Gulf War portfolio.

Ms. Marylyn Harris was impressed with the research but noted that there was no mention of taking care of the spiritual needs of Veterans. Dr. Ashford said that they do not have any specific programs for spiritual care, but every Veteran who enters their clinic is scheduled to see the chaplain to help provide that type of care to Veterans. In another vein, Louise Mahoney runs the yoga program in Palo Alto, and there is a spiritual aspect of that. Dr. Reinhard noted that at the WRIISC in DC, they had initiated a "moral injury" group. It was still preliminary, but it included a chaplain. And as Dr. Ashford said, their treatments are for the whole patient, including spiritual support, but it is not really a research project. Dr. Helmer mentioned that Dr. Steve Hunt held a PDICI webinar that included spirituality, and they have a pilot for spirituality in Veterans at the NJ site, although not specifically for Gulf War Veterans.

Dr. Young asked if they had studied the differential outcomes for patients in the WRIISC program and those not in the WRIISC program. Dr. Helmer acknowledged that the VA needs more closed loop processes; the WRIISC does follow-ups but not to the extent of comparing WRIISC patients to non-WRIISC patients. While they had not done this yet, the WRIISC is working on a Health Services Research project studying illness perceptions from conversations between Veterans and their providers. The hypothesis is that concordance of perceptions can affect patient outcomes. This project will generate data that looks at that question. Dr. Young was surprised that this kind of review had not been done. Dr. Ashford indicated that it is the one thing that has been lacking in the WRIISC. The WRIISC program is really very small. They have done research, clinical evaluations, and education but need to expand. They are not set-up to follow patients longitudinally. They are not really set up to care for Veterans, but

rather act as tertiary referral center. Dr. Ashford said that he can also send consults to Stanford professors, so the quality of the diagnostic work-up is excellent, but they don't have follow-up capability. He agreed that it would be important.

Mr. Bunker said that he frequently hears from Veterans who are happy with the care and information they receive at the WRIISC, but when they go back to their home VAs, their PCPs ignore the recommendations from WRIISC. He wanted to know what the Committee could do to help with that problem.

Dr. Helmer indicated that they are working very hard to improve clinical hand-off to integrate care between the WRIISC and local VAMCs, and trying to get social workers to communicate and be the contact points for follow-up. In research, they received considerable constructive feedback from reviewers when they submitted a proposal for an HSR&D research project to monitor the care that Veterans receive. They would like to be able to follow patients longitudinally, but that is not possible at this time because they do not know who the Gulf War Veterans are in the VA.

Dr. Hauser asked if they have a protocol for a "pre-visit workup" before patients come to the WRIISC, or if that is part of the assessment they do.

Dr. Ashford responded that they get 4 to 7 referrals each week. Nurses go through charts to figure out the problems and bring the necessary information to a team meeting. The team usually consists of a neurologist, neuropsychologist, social worker, nurses, an environmental specialist, and others as needed. The nurses present the case, and the group decides whether to bring the patient in, arrange a telephone consultation, or do an e-consult. Internal consults go to a neurologist, neuropsychologist, an anesthesiologist in the pain clinic, and a gastroenterologist. Every Gulf War patient goes to those four and probably gets an MRI scan, but if the patient has other symptoms, then he/she is sent to an appropriate specialist. The patient workup has to be finished in 30 days; failure to do so goes into a physician's performance evaluations. Generally the WRIISC does not request blood work unless there is a specific need. Additionally, they would not have another brain scan done if one had been recorded within the past year.

Dr. Helmer added that in the VA system they can see the whole medical record from primary care, so there is no need to re-run every test. They try to integrate all the information in the medical record to do their assessment. They even try to use clinical notes using natural language processing. The biggest challenge, though, is trying to identify Gulf War Veterans.

Dr. Hauser asked if they ever find previously unidentified, undiagnosed problem like multiple sclerosis or rheumatoid arthritis?

Dr. Helmer indicated that they usually do not. Typically they just try to give a diagnosis and answer patient questions. Frequently there are multiple contributing factors, so

follow-up is important and they try to work closely with the patients' PCPs. At six months, they find that at least one of their recommendations has been implemented.

Dr. Ashford said that only 1 in 10 patients has nothing new or interesting; approximately 1 in 5 has something new and dramatic. Half of their referrals are because Veterans go on the website and figure out how to request a consult; the other half are from frustrated PCPs who need help with a diagnosis.

Dr. VanLeeuwen commented that the WRIISC seems to use 5 or 6 specialists for consultations. He asked if being able to integrate research and clinical practice would help with Veteran health care. He also asked if there was another approach that would. Dr. Helmer said that it would be great if there were more environmental exposure champions. He would like to see better collaboration between researchers and clinicians, because that would make it easier to hand off patients from the WRIISC to local PCPs and advocates. He would like to see more deployment health clinics because they require a different level of knowledge and skills for making diagnoses of post-deployment health issues, a higher level than what a typical PCP has. Every provider needs to have basic information about GWI, for example. He added that every VA needs a provider who knows that the WRIISC exists, especially if there is no expert in deployment health.

Dr. Rauch asked if the three topic areas of the WRIISC vary by geographic region, i.e, if they work together or if the three sites have different emphases. He felt that a network of specialty clinics could support this model, and perhaps the different regions could focus on different areas. He felt that a "hub and spoke" model would work. He indicated that it seemed like there is a lack of organization, lack of thoughtfulness, for designing this VA wide, even though you the WRIISC staff work very hard and are excellent at what they do. He felt that the RAC is specifically charged to make the whole system work better, but it needs to be "top-down" and organized in a way that best delivers great clinical care. He wondered what were the RAC's opportunities for influencing a top-down decision. He also raised the question of autonomy at each WRIISC and that working together could make this work VA-wide.

Dr. Helmer gave some history of the WRIISC. The IOM produced a monograph about forming the WRIISC, with a broader, more systematic structure. VA sites competed, two were funded in 2001, and Palo Alto was added in 2007. The IOM report is available, and copies could be sent to Committee members. Since the beginning of the program, the design has gone back and forth between autonomy and a high degree of centralization. They are looking at different models for going forward, but no decision has been made. They are trying to harmonize while recognizing that each location has its strengths.

Dr. Ashford said that it is not clear how many WRIISC sites are needed. They have tried to harmonize their activities. The Directors meet two or three times per year. Program officers, IT staff, neuropsychologists at each site work together. The current model has been proven to be successful at VA.

Dr. Klimas said that VA has evolved over the years. She explained that, for HIV, there was a "train the trainer" program which was deployed throughout the VA. A curriculum was developed and implemented. She suggested that VA had since evolved into a two-tier primary care space - the PACT and the specialty care space - and you can envision Gulf War in either place. She wondered why there has not been a top-down command for PACTs to be a goal for primary care. She suggested that there should be a primary care team at every site, then the WRIISC can perform secondary care. It is nice to have algorithms for diagnosis, but Gulf War patients do not fit algorithms very well. Dr. Klimas would like for a Veteran to be able to walk into any VA and find someone who knows about Gulf War. She is concerned that the WRIISC training has not reached all primary care providers even though the WRIISC education program is very good.

Dr. Ashford indicated that they have tried to get social workers more involved at each site as a way to coordinate care. The WRIISCs have a proposal for all 168 VAs to get primary care teams for Gulf War, and they want to have webinars, then have local staff spread the word internally about the webinars and their content.

Dr. Klimas reminded everyone that as a research committee, they do not have too much "wiggle room" in making recommendations. There is probably a need for a clinical care committee because there used to be one. A directive letter would be needed to create a system like VA had for HIV.

Dr. Ashford commented that the conversations have been excellent. He also acknowledged the need for feedback from patients as suggested by Dr. Gazzaley earlier.

Dr. Reinhard indicated that it would be helpful if the RAC could help with recruitment of participants in research. He had heard from Dr. Kalasinsky that recruitment is an issue in many of the active research projects. VA is a large organization and needs a method of maintaining records nationally for recruiting; that would be a very useful thing for the Committee to recommend.

Dr. Crawford said that the Tampa VA is one of the largest, but there is nobody there who is a Gulf War expert. When she started collecting clinical samples, she had to go to some of the other VA's. It is difficult to increase recruitment when there is not an expert at a site.

Dr. Helmer agreed that we need to try to centrally collect the recruiting data.

Dr. Hunt said that only clinical research had been conducted thus far, so perhaps the new HSR&D research will help us figure a way to serve this group better.

Ms. Marylyn Harris said that we need to remind VA employees what the Gulf War was, and who are the Gulf War Veterans. It changed their lives dramatically. Many of the people she has dealt with at the VA for the past 20 years do not have any idea what she

went through. So we have to have accurate information to give to them to describe that era, and we need training on this. VA employees also need to understand the current challenges the Gulf War veterans face. She indicated that strategic alliances are important, too, to meet the VA research and treatment needs. More research is discussed at each meeting, but the people at the VA need to understand the needs of the Veterans. VA needs to talk to outside agencies, non-profit organizations, etc. about what the VA is trying to do in order to get partners interested in research.

Mr. James Bunker said that a lot of Veterans receive the Gulf War newsletter. He also receives a letter from the VBA regional office about what is going on in VBA, so he wanted to know why information about RAC meetings and recruitment could not be added to the Gulf War newsletter. He also suggested sending e-mail messages to everyone on the address list for the newsletter and sending information to the VSOs.

Dr. Helmer said that was a great suggestion. The WRIISC has been partnering with VSOs in the community around their area in New Jersey so they are not having trouble recruiting. Recruiting can be challenging, but they been able to meet their recruiting targets.

Dr. Wallin and Dr. Han Kang were involved in the DC WRIISC when it started, and it seemed like there were DoD data coming in. More recently at the MS center, they established a memorandum of understanding with the DoD. It should be possible to get the same kind of data with an MOU. Dr. Kang created a registry of 30,000 Veterans that could be used for a number of things, and it just required a few simple documents.

Dr. Reinhard suggested that this would be a good thing for the RAC to do.

Dr. Helmer said he was involved with the Burn Pit Registry, and the data are pretty good after 2001. They know approximately where people were. The quality of the data for Desert Shield/Desert Storm Veterans is worse because it has been so much longer since they were deployed. But one WRIISC project was able to get up-to-date addresses from DoD, so the DMDC roster was useful in recruiting.

Dr. Reinhard says it would be important to find out how useful those data were.

Dr. Hauser suggested that if the committee could help improve clinical care for GWI that would be a good thing for research and clinical research. He asked if the WRIISC Directors could give the RAC any help in suggesting recommendations – perhaps just that a clinical network should be set up.

Dr. Ashford said that he thinks it would be a harmonious response.
Perhaps the WRIISCs should expand, maybe add one in Minneapolis or Denver. By whatever mechanism possible, they need to get closer to the boots-on-the-ground Veterans, even if it is just to get a better registry. Doing this just for the Gulf War might be a little narrow, but doing it for post-deployment health could be beneficial to the whole VA.

Dr. Reinhard agreed with Dr. Ashford. WRIISCs are not required at all 168 hospitals, but there needs to be a person who is trained and who knows where to direct people.

Dr. Helmer added that because there are relatively few deployment health specialists for Veterans with GWI, a repository of information on the population would be very useful. Having a post deployment health clinic to identify brain cancer, ALS, etc., would be a very important resource for research and health care.

Mr. Bunker reminded everyone that the law covers everybody who served, but Desert Shield/Desert Storm is a much smaller number of Veterans.

Ms. Kimberly Adams (on the phone) suggested that as RAC members talk about research they might be missing the point about the quality of life for the Veterans. As Marylyn Harris said, the Gulf War affected her life, and Ms. Adams' own life, and it seems like the research is trying to figure out what happened to people. A lot of things can affect memory and other issues. Cognitive issues, pain, and other problems can cause someone's house to go into foreclosure, to cause bankruptcy, to cause family problems. She hoped that the committee also looks at the quality of life for the Veterans. When VA wanted to do something about homelessness, they sent a group of lawyers out to look into the problem to talk with providers to make sure that everybody was aware of the problem.

Dr. Hauser thanked Drs. Ashford, Helmer, and Reinhard for sharing their perspectives from the WRIISC. He encouraged anyone with ideas to contact the RAC (rac@ucsf.edu) or individual RAC members.

Committee Discussion

Hauser called the meeting back to order for the Committee to discuss the topics from the last day-and-a-half and possible recommendations for this year's annual report during the next 25 minutes.

Dr. VanLeeuwen passed out draft recommendations for committee consideration. The point was to discuss the draft recommendations for approval at a future meeting. They came from recommendations from Committee members, and there have been some minor changes to reflect the discussions of the previous day. The first recommendation has to do with the Gulf War Research Strategic Plan. There was interest on the Committee to have input. Some of the Committee recommendations that have been made in the past can be folded into updates of the research strategic plan. Integrating research into clinical care is also something that fits into the strategic plan. Since recruitment is a consistent challenge, there is a recommendation that the Committee could consider. Another addresses identifying challenges and suggests solutions regarding comparison groups as discussed in the previous meeting.

Dr. Tanner said that another aspect of research is education - educating Veterans about the value of participating in research to improve quality care, as well as educating providers.

Dr. Klimas said that some of this is addressed with the centers-of-excellence idea. A virtual training program can help create and deploy discoveries for clinical care purposes.

Dr. Hauser asked if centers of excellence would grow out of WRIISC centers or should they be something separate. He also asked if the RAC should think about five sites or one site or satellites that serve all 168 of the VA medical centers.

Dr. Klimas mentioned that at the VA you do not get credit for seeing patients outside of your VISN, and she wondered how the WRIISC accounts for their work. She concluded that it would take some retooling the way work is counted in VA or putting one center in each VISN. She preferred the latter option, with one per VISN. Currently, the local VAMC sites have to pay for the travel for patients to go to the WRIISC, so there is a reluctance to send people to the WRIISC because budgets are tight. If you're within a VISN, you can tap into special travel budgets - transplants, for example, have a special budget.

Mr. Bunker agreed that one per VISN is the better option because when you get out into the middle of the country where he lives, it is complicated to travel too far.

Dr. Wallin addressed the issue of identifying subjects for research and for follow-up. When the WRIISC was formed, they did a pilot study using a database to do mailings in the region, and there is no reason why the same cannot be done now. Making a nationwide database available online for recruiting would be very useful. Only 34% of Veterans use the VA healthcare system. Only 33% are eligible based on the amount of money they make.

Dr. Stephen Hunt wanted to follow up and reinforce Dr. Klimas' comment, and the things Dr. Rauch said earlier in the day had a big impact on him. There are a lot of resources in VA, so it would just be necessary to figure out how to integrate Gulf War issues into the post-deployment care.

Dr. Rauch was not sure what the scale is in the VA but comparing it to the private sector, he said that if there are 700,000 people meeting a particular standard across all divisions, then maybe it would be very difficult for 20 sites (one per VISN). He indicated that it would be better to have 150+ care sites that have the same standard of care, along with referrals up to another level. The Veterans who need to be recruited into studies might not want to make long trips from where they are to the closest VA center with the right expertise. Maybe four, five, or six WRIISCs should be set up and allowed to have a broader research portfolio. This kind of plan would still require a single education curriculum, a single registry, a single definition, a single name, and complementary work at the WRIISCs to achieve the goal.

For people not familiar with the VA system, Dr. Hunt added that there are patient aligned care teams (PACTs) that take care of Veterans, so you might want to have deployment health clinics at all VAMCs, then go higher to the VISN level and then higher again to the WRIISC level.

Mr. Bunker said that four years ago there was supposed to be just such a plan put into place, but he has not seen anything like that yet.

Dr. Hunt said that there is a lot of pressure in VA for access of Veterans for clinical care, so anything that the Committee can do to get providers to come to the community of care would be very useful to the whole VA operation.

Dr. Hauser asked what the cost would be for such a system. It seemed to him that the work RDUs are already there, and it would just be a matter of re-distributing assets.

Dr. Hunt indicated that sometimes it is difficult to find an hour to spend with a Veteran. He liked Dr. Rauch's suggestion that reallocating and restructuring would be the way to proceed. The primary care resources are stretched at VA, and the number one priority at VA is to get people in the door and give them diagnoses.

Dr. Wallin agreed with Dr. Hunt. The 30-day requirement to get people in and out with a diagnosis was driven by spinal cord injuries from the Vietnam era.

Dr. Klimas favored a primary, secondary, and tertiary care system, where the WRIISC would be the tertiary, and the VISN would be secondary. Since every VA is supposed to be virtual, it is important to remember that VA has "bean counting" inside the VISN but not outside the VISN. A primary care person in each hospital is a reasonable approach, but it is difficult to get secondary care at each facility. The WRIISCs need to be more accessible.

Dr. Hauser reminded everyone that Dr. Rauch mentioned a single database.

Dr. Klimas said that the Medicare complex reimbursement model under the ACA allows doctors to spend more time with patients. VA has not quite gotten there yet in her hospital. The doctors in the MS clinic can spend an hour with patients. She has permission to spend an hour with patients.

Dr. Hauser asked if there is a time-based billing system in VA.

Dr. Klimas said that RDUs are still being used and VA will probably be using them until the next system gets phased out.

Dr. Hunt indicated that the VA has primary care and specialty care. Dr. Klimas said that her specialty care clinic was turned into a primary care clinic, so VA can use the resources they have to force care into whatever model is necessary.

Dr. Klimas asked about the next meeting, and Dr. VanLeeuwen said that it will be either early next year or late this year.

Dr. Klimas brought up the section of the Committee charter that authorizes the formation of subcommittees. Dr. Hauser suggested that a subcommittee considering the center-of-excellence model outlined by Dr. Klimas in a draft that she shared sometime last year could be useful. Dr. Klimas said that she has the capability for treating Gulf War patients in her facility, and she wondered how it would be possible to make that kind of care more accessible across the VA system. That led to the idea of centers of excellence distributed around the country. She would like to see the model that was discussed earlier developed and sent forward.

Dr. VanLeeuwen reminded the Committee that they do not have to wait until the end of the year to submit recommendations; they can be sent to the Secretary at any time as long as they are approved by the Committee at an open meeting.

Dr. Klimas suggested that a working group develop a recommendation for centers of excellence that could be discussed during a conference call which is announced in the Federal Register.

Dr. Philbert asked how the suggestion of a clinical construct would be aligned with the RAC's research mission. Dr. Hauser said that a single broad recommendation that allows clinical research, translational research, and improvements in bedside care could be tied to the Committee's research goal. Dr. Philbert wanted to make sure that the ultimate desire of the recommendations is to improve patient outcomes.

Dr. Klimas said that DoD knows exactly who was deployed, but that information is not available in the VA nor is it searchable in the VA system. Even without an ICD-10 code for Gulf War illness, VA providers should be able to tell who has been deployed and not deployed.

Dr. VanLeeuwen suggested that subcommittees could be formed to address each of these issues, including the recruiting challenges.

Dr. Hauser suggested that the Committee might have more than one subcommittee focusing on the different aspects of the recommendations. He liked the idea of having a single umbrella recommendation with all the others falling under it.

Public Comment

Dr. Hauser asked Maj Denise Nichols, RN (USAF ret) to invite Veterans and other to make comments.

Ms. Nichols asked if there were any individuals who had not spoken the day before to come forward. She and Mr. Dean Lundholm had already spoken.

William Raymond Ziegler, Sergeant First Class (SFC), USA ret, said that something clinically significant happened out in the desert 26 years ago. He knew two months after his return that something was wrong. He implored the Committee to keep looking for solutions.

Dean Lundholm said that part of the frustration is that the Committee is "preaching to the choir" as the members are coming up to speed. There is a level of frustration because the Veterans have been doing this for many years, and they feel like they have to educate the committee. Once they get recommendations from the Committee, they have to go to their PCPs (who are usually nurse practitioners rather than MDs), and the Veterans have to tell the PCPs about the latest research. The PCPs do not necessarily accept that information. It is difficult for Veterans to explain their problems to nurse practitioners. The other thing he wanted to touch on was the WRIISC. There are lots of good outcomes from the WRIISC, and it is important to treat individuals differently because they may not all respond to the same medications in the same way.

Willie S. Green said that he was forced out of the military because of his health problems after the Gulf War. He had wanted to make a career of the army. All his health problems made them feel inferior. He felt like he had to fight harder here (with VA) than he did during the war. He hopes that his questions to the VA will make it easier for Veterans who come after him. His problems are not getting better, but they are not getting worse, except that everything gets a little worse as he gets older.

Ms. Nichols asked if anyone was on the phone. Since there was no response, she made a few comments. She said that there needs to be an announcement for the next meeting when there is a date and place. She would like more information about subcommittees, so Veterans can contact people and find out what the subcommittees are doing because they want to have input. VA research and CDMRP research could be posted on a website. She mentioned that Veterans have Facebook pages, and that the Boston VA has one. Ms. Nichols suggested that short videos on a webpage could describe research projects and tell Veterans how to contact the researchers. She is conducting some interviews with researchers for the radio, and she suggested that VA could make videos. Some of the presentations by the WRIISC could be special video presentations. She has been saying since 2002 that Veterans need to see the videos. She said that you can get lost on the VA website. The RAC website shows minutes and presentations, and she would like to have those prior to the meeting. Recruiting could be improved with short advertisements on the VA home page; short videos that Veterans can watch will interest Veterans, and contact information can be included. She is pleased that there is a doctor on the Committee now who served with her and the other Veterans as a flight surgeon. The doctors on the Committee can have a big impact training medical students at universities about the Gulf War, and maybe that would be another way to find new researchers.

Mr. Ziegler spoke again. He had failed to mention that he had a positive outcome with the WRIISC program. He finally received a diagnosis of a premotor polyneuropathy and brain dysfunction. He said there were good things going on at Palo Alto.

Ms. Nichols commented that the out-processing for the Guard and Reserves was done poorly after Desert Storm. She wondered if DoD had learned anything that helped Veterans of OIF and OEF. Veterans are reading Facebook pages. She also asked if Navy people who were on ships are they having problems. She suggested that if we want to have good research, we have to know what is happening with the new people.

Dr. Hauser thanked everyone for coming to the meeting, especially Veterans, and he also thanked Veterans for their positive comments about the WRIISC. He thanked RAC members for traveling to the meeting. He is confident that the discussions will lead to recommendations that will be meaningful.