# Research Advisory Committee on Gulf War Veterans' Illnesses

April 20-21, 2015 Committee Meeting Minutes

Department of Veterans Affairs
Washington, DC

**Research Advisory Committee on Gulf War Veterans' Illnesses**
**Boston University School of Public Health**
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I hereby certify the following minutes as being an accurate record of what transpired at the April 20-21, 2015 meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses.

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

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**Members of the Committee**
Stephen Hauser, Chairman
Roberta White, Scientific Director
James Bunker
Fiona Crawford
Beatrice Golomb
Nancy Klimas
Stephen Ondra
Frances Perez-Wilhite
Scott Young

**Acting Chief Consultant for Post-Deployment Medicine**
Ralph Loren Erickson

**Committee Staff**
Kimberly Sullivan, Associate Scientific Director
Brittany Sutton

**Designated Federal Officer**
Victor Kalasinsky

**Guest Speakers**
Lea Steele
Alvin Terry

**Institute of Medicine**
Roberta Wedge

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

**VA Office of Public Health**
Robert Bossarte
Erin Dursa

**VA Office of General Counsel**
Purnima Boominathan

**Veterans Health Administration, Deputy Under Secretary for Health for Policy and Services**
Madhulika Agarwal

**Interim Under Secretary for Health for the Department of Veterans Affairs**
Carolyn Clancy

**Secretary of Veterans Affairs Robert McDonald**

## Acronyms & Abbreviations

AA - arachidonic acid
ACh – acetylcholine
AChE – acetylcholinesterase
ALS – Amyotrophic lateral sclerosis
ATP – adenosine triphosphate
BChE – butyrylcholinesterase
CDC – Centers for Disease Control and Prevention
CMI – Chronic multisymptom illness
CNS – central nervous system
CO – carbon monoxide
CPF – chlorpyrifos
CPO – chlorpyrifos oxon
CSP – Cooperative Studies Program
DBQ – Disability Benefits Questionnaire
DEET - N,N-diethyl-m-toluamide
DFP – diisopropylfluorophosphate
DHA - docosahexaenoic acid
DOD – Department of Defense
DU - depleted uranium
GW – Gulf War
FDA - Food & Drug Administration
FY – Fiscal Year
GFAP - glial fibrillary acidic protein
GMPAC – Genomic Medicine Program Advisory Committee
GW – Gulf War
GWI – Gulf War illness
IOM – Institute of Medicine
IT – informational technology
LCV – Less common variants
LPC – lysophosphatidylcholine
MCS – multiple chemical sensitivity
MRI – Magnetic Resonance Imaging
MS – Multiple sclerosis
MWM - Morris Water Maze
MVP – Million Veteran Program
NRAC – National Research Advisory Council
OPH – Office of Public Health
ORD – Office of Research and Development
PB – pyridostigmine bromide
PC – phosphatidylcholine
PD – Parkinson's disease
PTSD – Post-Traumatic Stress Disorder
PER - permethrin

PON – paraoxonase
R&D – Research and Development
RAC – Research Advisory Committee
RFA – Request for application
SGE – special government employee
SM - sphingomyelin
SNPS - single nucleotide polymorphisms
VA – Veterans' Affairs
VHA – Veterans' Health Administration
WRIISC - War Related Illness & Injury Study Center

**Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses**
**April 20-21, 2015**

**Department of Veteran Affairs, 810 Vermont Avenue, Room 230, Washington, DC**
**(800-767-1750; access code 56978#)**

## *Agenda*
**Monday, April 20, 2015**

| | | |
|---|---|---|
| **8:45 – 9:00** | **Informal gathering, coffee** | |
| **9:00 – 9:30** | **Welcome, Introductory Remarks** | **VA Leadership** |
| **9:30 – 9:45** | **Welcome, Introductory Remarks** | **Dr. Stephen Hauser, Chairman<br>Res Adv Cmte Gulf War Illnesses** |
| **9:45 – 11:15** | **Gene-Exposure Outcomes in GWI and Committee Discussion** | **Dr. Lea Steele<br>Baylor University** |
| **11:15 –11:30** | **Break** | |
| **11:30 -12:45** | **Axonal Transport in Living Rats Exposed to GW-Relevant Pesticides and Discussion** | **Dr. Alvin Terry<br>Georgia Regents University** |
| **12:45 - 1:45** | **Lunch** | |
| **1:45 – 2:45** | **GW Agent Exposure Causes Impairment of Long-Term Memory Formation and Neuropathology in a Mouse Model of GWI** | **Dr. Fiona Crawford<br>Res Adv Cmte Gulf War Illnesses** |
| **2:45 -3:30** | **IOM Gulf War Panel Update<br>Program Update** | **Ms. Roberta Wedge<br>Institute of Medicine** |
| **3:30 – 3:45** | **Break** | |
| **3:45 – 4:30** | **Update of VA ORD Gulf War Research Portfolio** | **Dr. Victor Kalasinsky<br>Dr. Robert Jaeger<br>VA Office of Research and development** |
| **4:30 – 5:00** | **Million Veteran Program and GW Illness Research** | **Dr. Timothy O'Leary<br>VA Office of Research and Development** |
| **5:00 – 5:30** | **Public Comment** | |

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## *Agenda*
**Tuesday, April 21, 2015**

| | | |
|---|---|---|
| **8:45 – 9:00** | **Informal gathering, coffee** | |
| **9:00 – 9:45** | **Ethics and Federal Advisory Committee Training** | **Ms. Purnima Boominathan**<br>**VA Office of General Counsel** |
| **9:45 – 10:45** | **Update of VA OPH Gulf War Research** | **Dr. Robert Bossarte**<br>**Dr. Erin Dursa**<br>**VA Office of Public Health** |
| **10:45 – 11:00** | **Break** | |
| **11:00 – 12:00** | **VA GWI Research Program Discussion** | **Dr. Stephen Hauser, Chairman**<br>**Dr. Roberta White, Scientific Director**<br>**Res Adv Cmte Gulf War Illnesses** |
| **12:00 – 12:30** | **Public Comment** | |
| **12:30** | **Adjourn** | |

## DAY 1

### Welcome, Introductory Remarks
### VA Leadership

Chairman Hauser, neurologist and geneticist from the University of California, San Francisco, remarked that this was the first Research Advisory Committee (RAC) meeting that he had the honor of participating in and chairing. He introduced Secretary McDonald, who opened Day 1 of the April 2015 Research Advisory Committee on Gulf War Veterans' Illnesses (RAC-GWVI) meeting. The RAC-GWVI will be known as 'the Committee' going forward.

Secretary McDonald thanked Dr. Hauser for being willing to chair the Committee, thanked all of the Committee members for being present, and thanked the veterans for their service and contributions to the meeting. He also thanked new Committee members Frances Perez-Wilhite and Dr. Scott Young, a Navy veteran flight surgeon who joined the meeting by phone.

He noted that this meeting held significance because Department of Veterans' Affairs (VA) research and the Committee's work is of paramount importance not just for veterans, but for all Americans. The VA spends roughly $1.8 billion per year on research, a number he remarked as being too low in his opinion, because the research these funds support result in amazing breakthroughs for not only veterans, but for the American population . He cited a few examples of how VA research has had a positive impact on civilians including VA performing the first liver transplant and creating the shingles vaccine.

Secretary McDonald next discussed "My VA," an effort by the VA which is comprised of five strategies. The first strategy is to improve the veterans' experiences. The main goal of the VA is to care for the lives of the 22-23 million veterans in this country, with a focus on improving the daily experience for veterans that utilize the VA health care system and working with those in the private sector to improve veterans' experiences. The second strategy is to improve employees' experiences. Secretary McDonald stated that the VA must improve the employee experience in order to improve the veteran experience. He said that the VA is working hard to work with union leadership to change the systems that aren't working, improve the culture, and take responsibility for veteran screenings. The third strategy of "my VA" is to improve internal support systems such as informational technology (IT), which need improvement. The fourth strategy is to create a culture of continuous improvement and the fifth strategy is to form teaching partnerships. Secretary McDonald also stated that the VA has a moral obligation to work with our partners who have received honorable discharges.

Secretary McDonald said he believed that the 2014 VA crisis that occurred was not a result of the influx of Iraqi and Afghanistan war veterans, but was the result of Vietnam veterans, who are now sixty years old or older. He stated that in 1975 there were two million veterans over the age of sixty-five, but by 2017 it's estimated that there will be ten million veterans over the age of sixty-five, which will put a large demand on the system and indicates that the system needs to be improved to be able to have the capacity to accommodate our Iraqi and Afghanistan veterans in the near future. Secretary McDonald commented that the budget was a 7.5% increase from the House and the Senate and that he wanted to be a VA that works with the President and is ready to serve our veterans after war.

Secretary McDonald emphasized the need for the Committee to create clear, concise, and actionable recommendations for what elements of research the VA should take on. He commented on how the work of the Committee has a huge impact on what the VA does. For example, he said that they are already appropriating actions based on two prior reports. He commented that he looked forward to hearing about brain cancer and Gulf War Illness (GWI) recommendations as well as the results of two more important studies from the Institute of Medicine (IOM) on (1) brain and lung cancer in multi-symptom illnesses, and (2) epidemiological studies for Multiple sclerosis (MS) and neurological disorders.

Secretary McDonald concluded by saying that it is an honor to serve those who have served and that he looked forward to what this Committee would do under Dr. Hauser's leadership. He provided his contact information (Bob.mcdonald@va.gov).

Dr. Carolyn Clancy, Interim Undersecretary for Health at the VA, began by reinforcing the thanks to the veterans and the Committee and welcomed the new members of the Committee. She reiterated what Secretary McDonald had stated by recognizing that the contributions made by the Committee are very important. She drew attention to Denise Nichols, in attendance, who helped organize a listening session with her office. She stated that the goal of the Veteran's Health Administration (VHA) is to get the findings of research translated into practice seamlessly and much more rapidly (compared to an average of seventeen years from the time a research study is published to when it is used to benefit patient care). She stated that this was their strong commitment going forward because the VA has the capacity to make sure that the results of research and the recommendations made by the Research Advisory Committee (RAC) are translated to benefit veterans of the Gulf War (GW) and other wars. One thing she said she'd learned from prior positions is that what can feel like tension between scientists and clinicians is really a healthy, creative tension and that it is this shared commitment to patient care that will help to rise above the challenges. She thanked Ron Brown and others who have been tireless in their efforts on behalf of Gulf War veterans and for keeping the VA informed about what the public is concerned about. She said that she was looking forward to the upcoming presentations and public comment sessions.

Major Denise Nichols responded, noting that it was very encouraging to see Dr. Clancy's leadership two meetings in a row. Major Nichols suggested that the VA widely distribute the recent Committee report, which discussed translating research results to the clinical side. Dr. Clancy responded by saying that there was a strategic planning summit next week, which would provide the flexibility and resources to get veterans access to timely care and would improve the coordination of care with colleagues in the community.

Dr. Clancy commented that the infrastructure to get colleagues access to educational materials had been set up. She was confident that the expertise shared at the RAC would be spread much more broadly. Dr. Clancy stated that she would mention Ms. Nichols' recommendation there, where the network directors and senior leaders would be present to conclude what the logical "next steps" would be. The goal of spreading the Committee's research report widely was to inform those doctors and veterans who know very little regarding Gulf War Illness (GWI).

**Welcome, Introductory Remarks**
**Dr. Stephen Hauser, Chairman**

Chairman Hauser began by re-introducing the new RAC members, and he then asked each of the Committee members to introduce themselves. He read the scope of activity of the RAC on Gulf War Veterans' Illnesses from the charter, which states: "The Department of Veterans' Affairs Research Advisory Committee on Veterans' Illnesses provides advice and makes recommendations to the Secretary of Veterans' Affairs on proposed research studies, plans, and strategies related to understanding and treating the health consequences of military service of the southwest Asia theatre of operations during the 1990-1991 Gulf War (Operations Desert Shield/Desert Storm). [The Committee] shall meet in public session to review and advise the Secretary about VA funded research relevant to understanding and treating consequences of military service during this Gulf War…" He stated that this is the core of what the Committee is supposed to do. He again urged that the Committee needed to provide clear, concise, and actionable recommendations. Dr. Hauser commented that there were priorities in prior research that had not become actionable.

Thus, he declared that the goals for the next few meetings would be to (1) focus on the areas that were the "low hanging fruit" that could make an impact and in a very clear way and (2) push a few areas that he and members of the public thought were the most important to satisfy the mission of the charter. Dr. Hauser said that he believed the Committee needed to understand the fundamental cause of health problems and to be fundamental critics of the data, yet also to be moving what evidence the Committee had in order to implement the best possible improvements for those suffering. He stated that it is an honor for him to give back to veterans, and that he is available via email for questions. He provided his contact information: Stephen.hauser@ucsf.edu. He then called on the remaining Committee members to re-introduce themselves.

Dr. Hauser noted that this was the first meeting of the Committee since last fall when the Committee reorganized. He stated that the goals of the RAC for this meeting were: first, to learn about the most impactful new research in genetics and neurobiology, in order to focus on clinically important research at the next meeting; second, to review the current portfolios of research relevant to the VA RAC; and third, to begin to pull together an agenda for the Committee's goals for that year. Dr. Hauser announced that there would be two more meetings before September 30th, 2015.

Dr. Sullivan then introduced the first speaker, Dr. Lea Steele, to discuss recent research on gene-exposure outcomes in GWI. Dr. Steele is a past Scientific Director and RAC member who had just recently rotated off the Committee.

**Gene-Exposure Outcomes in GWI and Committee Discussion**
**Dr. Lea Steele**

Dr. Steele began the presentation by thanking the Committee for asking her to speak, having been at every RAC meeting herself since 2002. Additionally, she commented that the 25th anniversary of Operation Desert Shield was almost upon us. Before she began, she

acknowledged the work of the researchers on the panel and what they've done to help us better understand GWI. For the presentation slides of Dr. Steele's presentation, please refer to **Appendix A – Presentation 1**.

Dr. Steele mentioned that she would try to provide the information in the context of previous research of GWI and detail why specifically researchers should be interested in looking at this gene-environment interaction, keeping in mind that the new Committee members may not have read all of the previous RAC reports and may not be as familiar with other research related to GWI.

She began with a brief history of the Gulf War, providing information on important dates of Operation Desert Shield/Desert Storm. She commented on how it was a quick war, very different from our recent deployments, and that about 700,000 people served and that we won with relatively few casualties. However, despite the low number of casualties and the successful execution of the war, she stated that the troops came back with mysterious health problems now known as Gulf War Illness.

She rhetorically asked what had caused the health problems. She concluded that it was not merely the stress of war, but listed possible contributors including the trauma and stress of war, oil well fires, chemical weapons exposures, and the exposure at Khamisiyah (southeastern Iraq, early March 1991). At this site, she explained there was a massive munitions depot where our troops destroyed Iraqi munitions. She stated that we now know that there were chemical munitions in this "cloud" (most particularly sarin and cyclosarin) that formed after the demolition. She pointed out a Department of Defense (DOD) model of this cloud and the extent of this cloud's geography on a map to emphasize that as many as 100,000 troops were estimated to be exposed to low levels of these nerve agents just from this one incident. She also discussed pyridostigmine bromide (PB), anti-nerve gas pills, another contributor to GWI which was supposed to protect against the use of nerve agents. Dr. Steele also mentioned that there were multiple pesticides and insect repellants used to protect against serious diseases caused by exotic insects and flies in previous deployments. As many as 64 products were used during the GW, and fifteen of these have been identified by the DOD as pesticides of primary concern. At least 40,000 (DOD) troops were overexposed to high levels of pesticides. These represent just some of the exposures of potential concern for Gulf War veterans.

She summarized by concluding that the list of things that may have caused or contributed to GWI is long and that the RAC reviews the literature and looks at which factors are most important. She provided a summary of evidence from epidemiological studies, the findings of which are consistent with animal studies and what has been seen in other populations. The main points were that many epidemiological studies look at psychological stressors, but that consistent findings indicate that there is no association of this with GWI. Also, Dr. Steele stated that the evidence most consistently points to PB pills as well as excessive use of other pesticides as the likely main causes of GWI, although neurotoxins from chemical weapons, oil fires, and other chemical combinations can't be ruled out. She stated that other possible causes cannot be dismissed, such as vaccines, either because evidence is inconsistent or is limited in important ways. The conclusion was that the etiology of GWI is complex, so it is important to evaluate health outcomes in veteran subgroups.

Dr. Steele next discussed individual vulnerability to the adverse effects of neurotoxicants. She stated that people have long speculated that GWI is related to genetic variability. For example, she listed many studies that have been conducted on the enzyme paraoxonase 1 (PON1), which protects against the adverse effects of organophosphates. She shared what has already been learned from these previous studies and also commented on the limitations and noted that the inconclusive results were due to differences in study parameters, working definitions, and sample sizes.

She also mentioned butyrylcholinesterase (BChE), an enzyme that binds acetylcholine (ACh) inhibitors and thus also protects the body against the adverse effects of organophosphates. Dr. Steele concluded that there is a lot to know about this enzyme because there has been very little research done on it. For this reason, she designed her study around BChE. The central question in this study was whether GWI was associated with BChE enzyme activity or with the genotype of this enzyme. She acknowledged her collaborators and then provided some background on BChE, stating that researchers do not have a complete understanding of the function and activity of BChE. This enzyme provides a protective function against organophosphates and some other compounds. Interestingly, she also suggested that in some ways, BChE was our first understanding of pharmacogenetics, citing an example of how some people administered succinylcholine during surgery could not tolerate it and that this abnormal response was due to an inherited BChE deficiency. In her overview of BChE, Dr. Steele discussed the variants of the BChE gene. It is one gene with many variations, but the most common is the wild-type "U" allele, followed by "K" then "A" then "F" alleles. She mentioned that BChE serum activity can be a sensitive measure of the level of exposure to certain pesticides (that is, BChE activity goes down in presence of pesticides, so the degree of exposure can be gauged based on the level of BChE enzyme activity). Also, BChE at the time was being developed as a prophylactic measure to protect against nerve agents, which would make it a safer alternative to PB. It was thought that raising BChE activity would give protection against sarin.

Dr. Steele next discussed two reports which suggested that GWI may be associated with BChE. The first was a 1995 case report of an Israeli soldier, who had severe symptoms with PB pills during the Gulf War and was found to be a BChE AA homozygote. A second suggestion of a link to BChE came from a 1999 DOD project by Dr. Oksana Lockridge. Of the veterans reporting to have Gulf War syndrome, 73% were carriers of A or F alleles for BChE, while less than 30% carried the normal BChE allele. This was never published, but was an indicator that there may be a link between GWI and BChE.

Dr. Steele then gave a basic outline of her study focusing on BChE in relation to GWI. The goal was to determine if GWI risk was associated with cholinergic exposures overall and whether the risk differed by BChE genotype. They assessed BChE enzyme activity and genotype in a population-based sample of 304 GW veterans. This included 144 cases by the Kansas definition and 160 GW veteran controls. In the BChE subgroup analyses, they compared three groups. The first subgroup was UU (the most prominent genotype for BChE), the second subgroup was UK (the second most common genotype), and the third group represented the "less common variants" group (LCV).

The results indicated that the UUs and UKs had normal metabolism activity and were very capable of neutralizing acetylcholinesterase (AChE) inhibitors. The LCVs had an enzyme that acted more slowly and was less effective at neutralizing these compounds. Overall, BChE enzyme activity and genotype of GWI cases were similar to controls, so on the surface it didn't look like there was a connection.

Dr. Steele then provided results of BChE activity levels. Overall, for the GWI cases (144 cases) the mean activity level was 1.10 micromoles (mmol) and for Gulf War veteran controls (160 cases) the BChE mean activity was also 1.10 mmol. They were nearly identical but with slightly different standard deviations. From this, Dr. Steele concluded that the population-based samples effectively eliminated random variation.

Dr. Steele next discussed the results of the distribution of the BChE genotype. In the total sample, 62% had the normal UU genotype. She then looked at the proportion of the GWI cases that exhibited this genotype and the proportion of controls that were this genotype. Again, the proportions were almost identical between the two groups. However, when they combined all of the LCVs together, this genotype represented 10% of the GWI cases and 9% of the GW veteran controls. They next sought to examine the relationship between cholinergic exposures and GWI and see if that differed in the context of the BChE genotype.

She displayed a list of exposures and the corresponding risk factor for developing GWI. Researchers discovered that taking PB pills related to a 3-fold increased risk of GWI. This was a similar risk factor for pesticide exposures (except for being in an area sprayed with pesticides - her studies have consistently not found that to be a risk factor in GWI). She used 'hearing chemical alarms' as a proxy for possible exposure to nerve agents and in this study, this was not a risk factor for GWI.

Dr. Steele then presented a chart showing a preliminary indication of a significant gene-exposure interaction. The bar graph depicted the risk of GWI in relation to PB use, separated by BChE genetic subgroup. The data demonstrated that for veterans with slow-acting genotypes for BChE (28 veterans with this profile) and that used PB pills, the risk for developing GWI was 40.0 (which was highly significant from the other subgroups; for example, normal BChE genotypes were associated with an odds ratio of ~ 3.0). There was no interaction in the other genetic subgroups with PB pills and possible exposure to nerve agents.

Thus, the main finding of the study was evidence of a significant gene-exposure interaction between BChE genotype and taking PB pills in the Gulf War, with a subgroup of GW veterans with less active genetic forms of BChE who used PB pills at a significantly greater risk for developing GWI compared to other veteran subgroups. Dr. Steele mentioned that these were preliminary indications and that better sample sizes were needed, but that the results were still dramatic nonetheless.

Committee member Dr. Stephen Ondra asked what population size would be needed to do a statistically valid study, based on a power analysis. She answered that hers was statistically valid and had a highly significant finding. She mentioned that the association with PB was significant and the interaction itself was significant. The important concept was that there were no

differences between one subgroup and the larger population of GW veterans on anything except for BChE genotype, and that this was not just due to over-reporting of PB use. She answered another question regarding whether or not veterans in the smaller sample were in the same unit or just in the same location in the southwest Asia theatre. Her response was that it was a population-based sample based off of geographical area, so they were of different branches. This was just a grouping of a random sample.

Dr. Steele addressed whether these results could be an anomaly by using the Kansas GWI case definition (that is, whether they selected for veterans that had greater PB use). To account for this, they reassigned case status using the Centers for Disease Control and Prevention (CDC) chronic multi-symptom illness-based definition (a broader case definition), resulting in more cases than controls. Even though the CDC definition is broader, they saw the same pattern: there was an association in all GW veterans, but it was much more pronounced in the subgroup with slow-acting BChE genotypes. Thus, Dr. Steele's group was confident that this finding was not due either to factors related to the study or the case definition used.

To conclude, those with the slow-acting BChE genotypes are at a dramatically increased risk for GWI if they used PB pills, but not otherwise. These findings were consistent with two preliminary reports and two animal studies. This study provided preliminary evidence of a significant gene-exposure interaction, demonstrating that the subgroup of GW veterans with less effective BChE who used PB is at a greater risk of GWI. This was a small group of veterans, but the findings were very significant, so Dr. Steele said that this study should be replicated.

Dr. Steele also raised some additional questions. She mentioned that exposure to pesticides and other acetylcholinesterase (AChE) inhibitors lowerS the level of BChE in general. Researchers observed that people with the slow-acting enzymes had lower levels of BChE activity during the war and ever since. Thus, she wondered if perhaps others had lower levels of BChE during or after the war due to other AChE inhibitors they were exposed to and if they may pose to them an increased risk of GWI through similar mechanisms. These findings would have implications for animal models, yet she also cautioned that when assessing exposure in animal models, we need to keep in mind species differences in their enzymes.

The next part of Dr. Steele's presentation focused on the enzyme PON1, and whether differences in PON1 genotype were associated with Gulf War Illness. She described PON1, an enzyme which hydrolyzes (inactivates) organophosphates and other compounds such as insecticides and nerve agents. She described the two major variants of PON1: the Q variant is the most effective at hydrolyzing nerve agents, such as sarin, while the R variant is more effective at hydrolyzing some pesticides. She next showed her approach in an exploratory GWI – PON1 evaluation in a case-control study. Dr. Steele's approach was to study gene-exposure interactions as opposed to just genotypes in GWI cases versus controls.

The particular cohort in this study was all in one enlisted unit of the army and fell into units under the Khamisiyah plume (100% were exposed to oil well fire smoke). She found that those with at least one R allele exhibited a significant elevation in risk in developing GWI. Other risk factors included wearing pesticide treated uniforms for a week or longer, which increased the risk of GWI overall, yet those with an R allele were not at an increased risk for developing GWI

associated with wearing pesticide treated uniforms. Dr. Tim O'Leary asked whether the presented values had been adjusted for multiple hypothesis correction. Dr. Golomb commented, explaining that multiple hypothesis correction is not necessarily appropriate in cases where a relationship is expected, although this was exploratory research. In addition, those who took PB pills for a week or longer were at risk of GWI (interaction was significant).

Dr. Steele concluded by stating that this exploratory data showed that there is a relationship between PON1 and GWI, specifically in subgroups related to different exposures. This raised the possibility of gene-environment interactions which she thought should be investigated in the future. Dr. Steele stated that this type of approach is more useful and informative. Her results are summarized on page seven of **Appendix A – Presentation 1.**

Dr. Sullivan commented, stating that she agreed that this type of approach is very important and that it could lead to a strong recommendation made by the Committee, which would be that in addition to genetic vulnerability, studies should also include gene-exposure outcomes because it gives more powerful results. Dr. Klimas asked a question regarding gene regulation. She asked whether the day-to-day exposures that veterans now experience still play a role today in the persistence of the illness, and if so, whether anything can be done about that. That is, she asked whether anything could be done to promote detoxification pathways or whether the Committee could at least advise veterans to reduce their exposures and thus their day-to-day sufferings.

Mr. Bunker commented on his multiple chemical sensitivity (MCS). He described his personal experiences becoming ill in the presence of everyday household chemicals, such as chlorine, perfumes, and fabric softeners. Because of this, he suggested that avoiding chemicals and consuming antioxidants could potentially be helpful. He suggested perhaps it is the case that GW veterans obtained heightened chemical sensitivity during the war and despite certain chemicals having left the body since, the daily chemical exposures GW veterans are currently exposed to is perpetuating why veterans are still ill. He suggested that further research be done in this area.

Dr. Steele commented that it could be a recommendation that these veterans live a life in avoidance of chemicals in order to not exacerbate their symptoms, but that there haven't really been any studies on which to ground this recommendation.

Dr. Sullivan commented on Dr. Klimas' previous question and stated that there are some antioxidants that alter PON1 and that research was ongoing in this area. She was unsure whether such research was being done on BChE. Dr. Ondra also commented that research into these areas would be very useful because, given finite resources, making the case that such treatment research opportunities extended beyond the intended population of GW veterans and to the civilian population and those who will serve in future deployments as well makes it a more compelling case to spend the resources in these areas due to the scale and scope of the affected. Thus he recommended research in how to manage other potential toxic exposures and predict those people who are at risk.

Dr. Hauser asked a few questions, which included: (1) How can the Committee make the case that this an incontrovertible association? (2) Why not sequence the protein (including exons and introns) and get the whole range of variants? (3) Is the 192 variant of PON1 associated with rare

Amyotrophic Lateral Sclerosis (ALS) cases? Given that the ALS literature was shortly after the war, is there genetic material from that population to look at?

Dr. Steele responded to the questions as follows: (1) To make the case an incontrovertible association, a larger population would be needed along with a clean case definition and the best ascertainment of exposures; (2) For the rarest variants of PON1, they would not be able to attain a decent sample size; (3) Yes, in the early 2000's, an ALS registry was established that included GW veterans and those samples could be genotyped.

The Committee concluded that in addition to looking at vulnerability factors, resilience factors should also be examined. It could be the case that the controls (those who were exposed and did not get sick) have some resilience factor or also that certain veterans with less exposure are more adversely affected due to other genes amplifying the effects of the exposure. In summary, from the gene-interaction results Dr. Steele presented, the Committee came to the consensus that gene-exposure outcomes are important, not just in identifying genetic subgroups but also when considering levels of exposure.

The Committee took a fifteen-minute break before reconvening for Dr. Alvin Terry's presentation.

**Axonal Transport in Living Rats Exposed to GW-Relevant Pesticides and Discussion**
**Dr. Alvin Terry**

Dr. Sullivan introduced Dr. Alvin Terry, whose research interests focus on the role of central acetylcholine (ACh) or cholinergic pathways in cognition and how these pathways are involved in memory dysfunction, primarily regarding exposure to environmental toxins (organophosphates in particular). For the presentation slides of Dr. Terry's presentation, please refer to **Appendix A – Presentation 2**.

Dr. Terry began by thanking everyone for giving him the opportunity to speak. He provided a background and overview of the work he and his colleagues had been doing. He first provided a brief overview of the central cholinergic system of the brain including circuits, roles, and projections to other brain regions. He stated that these areas are well known to be involved in cognition. Another major focus of his lab is on organophosphates, which are well known to affect the cholinergic system. He gave a brief history on the use of organophosphates and how their use evolved to be used as nerve agents. He touched on the prevalence of these compounds, stating that they are found in insecticides and chemical warfare agents.

He displayed a diagram showing how organophosphates work (which is by binding and inhibiting acetylcholinesterase, causing ACh buildup in the synapse). He detailed the symptoms resulting from acute exposure to such agents, both at low and high levels of exposure. Diisopropyl fluorophosphate (DFP) is used because he stated it has a very similar structure to sarin but is less toxic (less potent). He described that what is less understood is the effects of repeated exposures to sub-threshold doses: that is, doses that are not associated with acute toxicity. There have been a number of epidemiological toxic studies that would correlate a variety of behavioral symptoms (such as psychotic symptoms) with this lower level of exposure,

but he stated that the caveat is that most of these studies were correlational. Dr. Terry believed animal models are needed to study the long-term effects, yet he acknowledged that it's difficult to say that this is the only cause of illness when we know there are multiple factors that resulted in Gulf War Illness.

The overall objectives of his study were to: (1) look at the consequences of repeated, subthreshold exposures and determine its effects on different domains of cognition, and (2) determine the consequences of these types of exposures on substrates of cognitive function. He asserted that it was first important to make the argument that these lower level exposures indeed lead to memory-related deficits and if so, to then determine the mechanism. He stated that patients would be treated better if this is known. The goal would be to identify therapeutic targets to provide viable treatments. He mentioned that there are several different potential mechanisms, but today he concentrated only on axonal transport.

He presented a list of organophosphates that are known to have been used in the GW. There have been many studies linking exposure of organophosphates to the neurological symptoms of GWI. He highlighted some of the different papers his lab had published in order to present the argument that subthreshold exposures to organophosphates cause memory deficits. Then he began to delve into the mechanisms.

He explained one behavioral task, a five-choice serial reaction time task, which is a measure of sustained attention. There are various items that can assess attention performance. He stated that one can effectively train a rodent to do this task in an operant chamber. He then depicted the results and conclusions of an experiment utilizing this behavioral task, showing a few slides from a paper he published in 2010. The organophosphate chlorpyrifos (CPF) was administered every other day to rodents at a subthreshold dose (18 mg/kg). Animals were first trained until they could achieve ~85% correct in the attention task. When administered a vehicle, animals had the same accuracy correct, but in animals exposed to CPF, the performance accuracy decreased over the course of 30 days. Even after 30 days of recovery (no CPF administration), they never fully recovered (although the performance did improve somewhat). Another notable finding from this study was that in animals exposed to organophosphates, there was an increase in premature responding which persisted across the 30 days. In another experiment, animals were given a threshold dose of DFP and then were allowed to recover over 30 days. Dr. Terry stated it may be the case that lipophilic insecticide types of organophosphates like CPF linger longer in the brain, while nerve agents at this lower level may have activity that doesn't last as long. A finding from this experiment was an increase in timed out responses. The conclusion was that repeated, low-level DFP exposure led to impairment in sustained attention.

He then recounted the findings of another paper. In this study, researchers used the Morris water maze (MWM), a classic spatial learning task. He described the setup. This study examined a couple different doses of sub-threshold exposures (again for 30 days). Normal control animals learned the maze quickly, achieving a latency to complete the maze of ten seconds after five days. Dr. Terry noted that CPF, DFP, and organophosphates did not cause motor damage in the animals it was administered to, therefore not impairing the physical ability to complete this type of task. They administered these drugs to the animals, and then switched the location of the hidden platform for a "relearning" phase, to test cognitive flexibility. The results were as

follows: Animals administered CPF didn't have any problem with the task, while conversely those administered DFP over a 30-day period (receiving subthreshold exposure doses every other day) exhibited fairly robust impairment. These animals had deficits in learning the location of the platform. The conclusion was that organophosphates and DFP may cause chronic deficits in memory long after cholinesterase inhibition has evaded, and that insecticides and nerve agents may have differential effects on cognition.

Dr. Terry cited a paper which had demonstrated that high doses of a neurotoxic agent resulted in a decrease in axonal transport of neuronal growth factor. This provided evidence that environmental toxins affect this fundamental component of neuronal function. He transitioned to describe a series of experiments conducted in rats. He detailed his study's experimental design. They administered similar doses of CPF in rats and then removed their peripheral sciatic nerve and viewed it under a microscope. They found that axonal transport in the retrograde and anterograde directions were inhibited and that this effect lasted up to fourteen days. He then discussed axonal transport, how it's a fundamental process in neurons, and next gave an overview of how it works. He highlighted the microtubule system and iterated how this is very important for axonal transport. He then described it in further detail, explaining that the motor protein kinesin is best characterized at moving molecules in the anterograde direction along a neuron and that the motor protein called dynein is responsible for moving materials in the retrograde direction (back to the nucleus of a neuron). All of this is critical to the proper functioning of a neuron. He showed a diagram of the microtubule system and discussed its formation. He stated that a hypothesis is that reactive molecules such as organophosphates can bind covalently to kinesin and affect its activity or affect the tubule polymerization process, that is, the formation of microtubules.

The first thing done in his studies was to examine cultured neurons where movements of mitochondria were monitored using Mitotracker. He showed photographs of the labeled mitochondria, pointing out the robust change in their elongation system. He showed an overview of the results of that paper. Essentially, the morphology of mitochondria as well as their transport changed when exposed to the CPF chemical and its metabolite, chlorpyrifos oxon (CPO). In addition, he conducted several fluorescence studies to demonstrate that these effects on mitochondria were not related to just non-specific damage to the mitochondria or to the neuron. They also conducted studies on adenosine triphosphate (ATP) and superoxide, among others. In summary, they examined a concentration-dependent decline in the transport of mitochondria, an increase in their length, and a decrease in their numbers. They demonstrated that these changes weren't related to other problems in the cell such as ATP problems, mitochondrial membrane problems, or problems with superoxide production. Dr. Terry would be following up on this study with others in the future.

Dr. Terry announced that his team had put together a new model with the help of a collaborator, who had created a version of the amyloid precursor protein. They tied this to a fluorescent molecule. He continued, describing a few ways fluorescent labeling can be achieved. His research team used time-lapse imaging to monitor the movement of these proteins, which he said can be measured very accurately (in microns traveled per unit of time). They first used a positive control (colchicine, known to impair tubule polymerization) to create a concentration-effect curve and validate their model, demonstrating that they could measure impairment by a positive

control. Then, the next series of experiments he described used DFP, a nerve agent similar to sarin.

In the next series of experiments which used DFP, Dr. Terry saw a very similar profile; that is, a decrease in axonal transport in both the retrograde and anterograde directions. His team used muscarinic and nicotinic agonists in order to demonstrate and confirm that this effect was not related to cholinesterase or some other cholinergic effect.

Dr. Klimas asked a question regarding whether a stress event was included to transform the acute model to a chronic model. In regards to stress, Dr. Terry answered that his studies did not use corticosterone, although it could be applied in a culture model or in a stressful event in an animal model. Dr. Klimas assumed that corticosterone would affect axonal transport, but Dr. Terry hadn't seen axonal transport studies which have used it and did not seem to think it would largely affect axonal transport.

His research team examined cell viability within a certain assay. He displayed slides of different stains they had used. The results indicate that there was no change in the morphology of the cytoskeleton. He stated that he hoped to publish these results which indicated that DFP impairs axonal transport.

Next, he began describing his Magnetic Resonance Imaging (MRI) studies. He adopted a technique called "manganese enhancement magnetic resonance imaging." He discussed the specific properties of this technique and discussed the pathway they were using. He provided an overview of the well-known visual pathway they used for these studies. He stated that this was a very well-documented circuit which has been used in the literature to show transport deficits. His team adopted this method to look at what organophosphates might be doing to such transport mechanisms.

In these studies, they delivered a subthreshold dose of CPF acutely, giving injections of manganese and CPF in the eye. He commented that the results were somewhat surprising compared to the results they achieved when injecting CPF to the sciatic nerve. The next series of experiments involved a 14-day repeated exposure to CPF. They took baseline measurements, exposed the animals to CPF for 14 days, then 24 hours later conducted imaging and then finally did another round of imaging 30 days later. The results indicated that there were statistically significant impairments at a dose of 3 mg/kg and up to about 4 mg/kg, yet the higher dose was not statistically significant, which was surprising.

The conclusions were that injections of a positive control validated the techniques used in their lab and that single subcutaneous injections of CPF did not appear to affect transport but then conversely, repeated subthreshold exposures did cause impairment. He gave an overall summary of all of the work he had presented thus far, concluding that repeated subthreshold exposure to both pesticides and nerve agents leads to prolonged impairments. He stated that they may have differential effects, for example lipophilic compounds remaining in the tissue for longer periods than more reactive compounds. He commented that there were many hypotheses and postulated a mechanism. He next discussed future studies and the future directions of his lab as well as other possible targets of organophosphates that could be examined (such as tubulin acetylation). He

thanked the Committee for their attention and then took questions.

Dr. Sullivan commented, putting Dr. Terry's work into context by saying that previously it was thought that if one didn't exhibit acute cholinergic poisoning from pesticide and/or nerve gas exposures, that there were no chronic effects. Yet his work systematically demonstrated through cellular, behavioral, and the current tracing studies in a live animal that that is not true. She also acknowledged that animal studies are critically important, given the fact that these exposures are very relevant to GW veterans yet research projects of this nature can't be done in veterans. She commented that seeing effects 30 days later in a rodent after an exposure translates to many years in a human when the life span of a rodent is accounted for.

In terms of investigating a treatment, Dr. Terry would begin to examine compounds for treatment in a cell culture environment. Further down the road, he would begin to examine the effects of combinations of exposures.

Dr. Golomb commented that she knew of a recent study in the fish or eel where the researchers demonstrated protection against the acute and chronic effects of organophosphates by application of certain antioxidants just before or after exposure. Thus, she asked whether Dr. Terry had identified any other mechanisms such as oxidative stress that could be an indicator of toxicity. Dr. Terry responded that he had not, but that other groups were looking at oxidative free radicals.

Dr. Crawford asked whether he was planning to do any ex-vivo work. He responded that he was planning this approach.

Dr. Hauser thought that Dr. Terry was using ATP as a visualization marker for staining, so he asked whether stained aggregated ATP could be used as a way to visualize axonal transport. He asked this because he was thinking about a pathology that could be deployed to human tissue to see if a similar axonal transport pathology could be found in humans. Dr. Terry responded, saying that they'd done such stains in rats and then he displayed the results of his unpublished study.

Dr. Klimas asked how the subthreshold dosages used in these studies related to real dosages and exposures. Dr. Terry replied that they were more relevant to agricultural workers, pesticide applicators, GW veterans, and others with occupational exposure. The subthreshold doses were higher than trace amounts (normal environmental exposure) but below the level associated with acute toxicity.

Dr. Hauser commented that he didn't think PB could penetrate the central nervous system (CNS), so asked whether there were subtle changes in axonal transport visible as a result of PB exposure. Dr. Golomb commented, stating that exposures to ACh inhibitors that cause oxidative stress could make the blood-brain barrier more "leaky" and thus exposures to such compounds on a repeated basis may facilitate these toxic compounds such as PB into the CNS.

With that, the questions and comments on Dr. Terry's presentation concluded and the Committee moved on to a presentation by Dr. Fiona Crawford.

**GW Agent Exposure Causes Impairment of Long-Term Memory Formation and Neuropathology in a Mouse Model of GWI**
**Dr. Fiona Crawford**

Dr. Sullivan introduced Dr. Fiona Crawford, President and CEO of the Roskamp Institute in Florida. Dr. Crawford is a molecular geneticist by trade but had focused on Alzheimer's disease which led her to study GWI. Dr. Crawford commented on the complexity of GWI compared to Alzheimer's, but also mentioned that the approaches used to research Alzheimer's could also be used to develop a treatment for GWI. For the presentation slides of Dr. Crawford's presentation, please refer to **Appendix A – Presentation 3**.

She discussed her preclinical model, the mouse, and explained the advantages to using this species. Some of these advantages include cost, replicability, and that they can be genetically modified.

She outlined her general approach, which was to develop mouse models of exposure to known GW agents such as PB and permethrin (PER). She commented that there are many models, which there should be in order to capture the heterogeneity and etiology of GWI. She stated that her lab uses various paradigms to characterize the models, including neurobehavioral (rotarod, a measure of motor function), the Barnes maze (dry version of the Morris Water Maze for learning and memory), neuropathological analyses, and molecular profiles. Her group relies strongly on clinical collaborators and what they learn from GWI presentation. The goal was to develop a model that recapitulated certain aspects of the illness so that they can know they're focusing on something relevant.

She transitioned into describing some of the models they had already developed and what they were currently focusing on. She commented that it is difficult to publish animal studies of GWI due to critiques of the animal models and thus, they need to ensure there are platforms where this unpublished yet interesting and important data can be shared. One of the reasons they had been criticized for was high doses, but she argued that this was required in order to see a phenotype (an effect) in mice. Also, Dr. Crawford knows that this is what happened to GW veterans in theatre: multiple exposure levels. She commented that even if it did not cause immediate acute toxicity, as long as an agent was considered to be relevant and was in exposure levels that GW veterans experienced, that it is important and useful to monitor what it does to a rodent model over time.

Her first model was one of PB, PER, the chemical N,N-diethyl-m-toluamide (DEET), and stress, adapted from the work of Dr. Abdel-Rahman. They delivered 1.3 mg/kg PB orally, 0.13 mg/kg PER dermally, 40 mg/kg DEET dermally, and presented five minutes of restrained stress. They next tested the mice for anxiety in the open field test and also used a rotarod and the Morris Water Maze (MWM). The results indicated there were anxiety effects after twenty days of exposure but there were no effects on cognition. Also, there were some effects on pathology, in that exposed mice exhibited a significant increase in glial fibrillary acidic protein (GFAP) indicating astrogliosis.

The next model looked at mice exposed to a combination of PB and PER (permethrin) at nine

weeks old. She summarized the experiment timeline/preclinical platform and commented that their goal was to look at extensive time points because it was then 24 years later for GW veterans. She displayed the open field test results and explained that mice were evaluated in a fifteen minute period, with their performance in each five minute period blocked. The total distance traveled and the time spent in the perimeter was recorded, as this serves as a measure of anxiety. They found that by day 30 (one month after exposure), the exposed mice spent significantly more time in the perimeter than controls, suggesting some anxiety behaviors. They also traveled much less, migrating to a wall and then staying there. She then displayed the results of the MWM. To summarize, over time the exposed mice had decreased cognitive performance. When they examined GFAP neuropathology, they found a similar effect to what was seen in the PB-PER-stress model. That is, an increase in GFAP in exposed mice compared to controls. Five months after the initial 10-day exposure, researchers detected what proteins were present in exposed and unexposed mice, how the protein expression level changed, and used software to elucidate the anticipated functional effects of such protein changes (for example, how it relates to inflammation or mitochondrial function). She displayed her data showing the proteomic changes in the brain and the blood. These corresponded to changes in biological functions of the brain and plasma modulated in response to PB+PER exposure. The lipid metabolism, molecular transport, cell death, cell cycle, inflammatory responses, immune responses, inflammatory markers, and lipid metabolism were significantly different in GW agent-exposed mice five months after exposure. Dr. Crawford stated that this mouse model could be used as a model for the human condition of GWI.

In another pilot study, Dr. Crawford examined exposure to CPF, administered alone or in combination with PB and PER. The mice were euthanized at 3 days post-exposure for neuropathological analyses. She found differences in all three groups when looking at markers of neurogenesis, synapse activity, and synaptic function, observing a significant reduction in both CPF alone and CPF in combination with PB and PER. She also observed differences in astrocytes when comparing between groups. Nothing significant was observed when using IBA-1 to stain for microglial activation, a marker for neuroinflammatory pathology. This finding was consistent in their models at the five month time point. The fact that her team observed astrocyte activation and not microglia activation was very surprising and interesting. Dr. Crawford stated that this difference was likely important and she commented on the current lack of understanding of the function of astrocytes.

Dr. Crawford next described their translation from using the CB1 mouse strain to the C57/B6 mouse strain, which is more commonly used in research. The dose was slightly modified. The goal was to mimic the experience of GW veterans by acute exposure to GW agents at a young age and then evaluating longitudinally over the lifespan of the mouse. They evaluated at five months, 15-16 months, and 22 months.

Dr. Crawford found no acute differences in GFAP staining after exposure. That is, there was no increased astrocytosis ten days after the 10-day exposure regimen ended. However, at five months post-exposure, they found significant increases of GFAP in both the hippocampus and cerebral cortex. They also found an acute effect (seen at 10 days post-exposure) of reduced markers of neurogenesis and decreased synaptophysin (a marker for synaptic function). The reduction in synaptophysin was still present five months after exposure.

They next assessed cognitive performance in this mouse model. At 15-16 months, mice exposed to PB+PER took significantly longer to find their way in a water maze. These cognitive effects in this mouse model were persistent at five months as well. (The data from the Barnes maze at age 22 months was not very useful because the mice were so old at that age that they just had trouble completing the task.)

Dr. Crawford next described her proteomic profiling work. They took the brains of mice from the five month timepoint and 16 month timepoint and examined which biological functions were significantly modulated in the model. They found their three key areas of interest to be immune/inflammatory function, mitochondrial dysfunction, and lipid metabolism. Her data also showed the persistence of astroglial (inflammatory) pathology across the mouse lifespan (all three timepoints) in the cerebral cortex. In the dentate gyrus of the hippocampus, this increased astrocytosis persisted at a significant level at 16 months but was no longer significant at 22 months.

Dr. Crawford next described the disruption of mitochondrial proteins in mice exposed to the GW agents PB+PER. They applied an antibody-based approach, labeling against cytochrome-c oxidase, subunit Vic, and observed a significant reduction in mice exposed to PB and PER compared to controls. They examined another protein (ubiquinol-cytochrome-c reductase core protein 1) and saw a reduction in this protein in exposed mice as well. They next examined mitochondrial function as a measure of cytochrome-c oxidase activity and found a significant decrease in cytochrome-c oxidase activity in the PB + PER mouse. Cytochrome-c oxidase is the final step in the electron transport chain – its activity is thought to be a good indicator of metabolic capacity required for normal function in neurons. Their proteomics evidence showed that this was significant at the 5 and 16 month timepoints.

Dr. Crawford emphasized the utility of lipid analyses. Lipidomic data uses internal standards, so can provide an actual value as opposed to relative amounts of the lipids in question. In developing the lipid profile, they found that phosphatidylcholine (PC) and sphingomyelin (SM) were significantly increased in the brains of PB+PER exposed mice (at 5 months post-exposure). Catalase staining at 5 months post-exposure showed that in the dentate gyrus, peroxisomes were upregulated in exposed mice. At 16 months post-exposure, there were some differences. Some lipids' concentrations went down, including PC and SM, which were increased at 5 months post-exposure. Dr. Crawford noted that this had been reported in other conditions too like diabetes, where there is an early accumulation of phospholipids which deteriorates over time. Dr. Crawford also noted that the mice exhibited significant weight loss at this time point, which was also indication that lipid metabolism is likely playing a role. Dr. Golomb asked Dr. Crawford if she assessed whether the weight loss was due to fat loss or whether it was due to muscle or bone loss. Dr. Crawford responded that she did not examine this, but agreed that it would be good to do so.

In this mouse model, they also observed a decrease in free fatty acids in exposed mice as opposed to controls as well as a decrease in other metabolites. The arachidonic acid (AA) to docosahexaenoic acid (DHA) ratio was increased in exposed mice. She then went into some detail about the role of omega-3 and omega-6 fatty acid-containing lipids in human health. AA

(an omega-6 fatty acid) and DHA (an omega-3 fatty acid) are essential fatty acids primarily acquired through diet, owing to the low capacity of the body to synthesize these lipids. Dr. Crawford stated that in general, fatty acids that contain AA are associated with pro-inflammatory responses, whereas DHA metabolism produces anti-inflammatory metabolites. Dietary intake of DHA is particularly important in aging adults in order to maintain cognitive function and for optimal neurotransmission. At both 5 months and 16 months, the shift in AA/DHA imbalance in the exposed mice was the same (compared to the lipid metabolism which increased but then decreased by 16 months). This chronic imbalance of AA and DHA in the exposed mice correlated with astroglial pathology. She showed pictures of the astroglia pathology in the cortices and dentate gyri of the exposed mice.

She next discussed her hope in the lipidomic data for developing a biomarker for GWI because researchers could identify the normal range and subsequently identify when patients are out of the normal range. She also addressed an exciting intervention in lipid metabolism problems, which is a dietary change. She displayed plasma PC and lysophosphatidylcholine (LPC) profiles eighteen days following GW agent exposure. They found a significant decrease in LPC in the blood of exposed animals. At 5 months post-exposure, there was also a trend for a decrease of PC and LPC in the blood. At 16 months, the decrease in PC and LPC was again significant. Throughout the longitudinal evaluation, they observed the prevalence of many individual lipid species decrease. Dr. Crawford suggested that this is an area that needs a lot more research to determine if any of these lipid profiles could serve as a biomarker for GWI. She determined that large population sizes would have to be used to determine a profile specific to GWI.

To summarize, Dr. Crawford stated that from the mouse studies, we do seem to have some plasma biomarkers of exposure to GW agents that are evident at chronic timepoints. She was very optimistic that researchers would soon find plasma biomarkers for GWI. In addition, characterization of these mouse models of GWI identified a number of potential therapeutic targets for further evaluation, including inflammatory responses, lipid dysmetabolism, and mitochondrial dysfunction.

To target inflammation, her team was studying anatabine, a tobacco-derived compound that is a potent anti-inflammatory compound and has efficacy in other conditions such as Alzheimer's disease. They waited until 5 months after exposure, treated with anatabine, and saw significant improvement in cognitive function in the PB+PER mouse model of GWI. This improvement was also reflected in the GFAP pathology in that anatabine treatment significantly reduced astrogliosis in these mice.

Dr. Crawford concluded the presentation by overviewing her clinical studies of plasma biomarkers of GWI. She had collaborations with Dr. Krengel, Dr. Sullivan, and Dr. Golier. For these studies, they were collecting blood samples for proteomic and lipidomic profiling and performing targeted analyses. She stated that they would continue their work with the mouse models and continue to validate therapeutic targets. She stated that these efforts were facilitated by collaborations between GWI clinical and basic science research teams. She also said that she was very optimistic about moving forward because the GWI field is much more collaborative than past fields she'd worked in. She gave her acknowledgements and began taking questions.

Dr. Sullivan asked whether the blood samples that were examined were plasma. Dr. Crawford stated that indeed they were plasma samples. Dr. Golomb commented on how she had also found profound alterations in lipid biomarkers and stated that metabolomics were primarily driven by lipidomics. In her opinion, this re-enforced the relevance of Dr. Crawford's findings.

Dr. Hauser asked a question regarding serum markers. He asked how reliable the samples were throughout the course of the day, given the effects of medication and other confounders. Dr. Crawford responded that there certainly would be confounders and that they had strict standard operating procedures they followed in the collection of samples to try to mitigate their effects. She stated that if patients were fasting when they provided the sample and that there were enough samples to account for other variables, then the effects of confounding variables would be minimal. Dr. Golomb commented that the factors that Dr. Hauser was concerned about being confounding variables were likely just sources of variability, because unless they are different from controls then they are not confounding but just sources of variability that alter the statistics. She stated that if Dr. Crawford was recruiting and seeing controls and veterans in the same way that they were likely not confounders.

Dr. Klimas noted that the more the samples are restricted (by exclusion criteria), the less representative the sample is of the population. She suggested that rather than be worried about confounders, to instead include more people and ramp up the population sizes, which would then better encompass the complexity of the population.

Dr. Sullivan asked whether some of the effects they found could be related to permethrin exerting different effects than organophosphates since it has a different mechanism of action than organophosphates. Dr. Crawford responded, saying that she didn't think her PER exposure was extreme given the exposures in the field that veterans had as she was aware. She also again stressed the need of multiple models of exposure, including different exposures and different paradigms, in order to provide treatment for all.

Jim Bunker stated that while some uniforms may have been coated in pesticides, others were not. For example, his did not and in addition he washed his uniform by hand. This reflection highlighted how veterans had different exposures and different dose ranges.

**IOM Gulf War Panel Program Update**
**Ms. Roberta Wedge**

Dr. Hauser introduced Ms. Roberta Wedge, senior program officer at the Institute of Medicine.

Please refer to **Appendix A – Presentation 4** for the slides of Ms. Wedge's presentation. She first provided an overview of the IOM as an organization and their approach, stating that the Institute of Medicine asks and answers the nation's most pressing questions about health and health care. They are an independent, nonprofit organization that works outside of the government and provides unbiased and authoritative advice to both decision makers and the public.

Their goal as adviser to the nation is to improve health. She noted that the IOM's

recommendations are always evidence-based and that some of the ways they operate in order to achieve their goal is to provide a neutral venue for open dialogue and discussion. She then provided an overview of the origin of the Gulf War and Health Series, including the three laws that empowered the IOM to conduct the studies requested by the VA regarding the health of veterans of the Persian Gulf War (Veterans Programs Enhancement Act of 1998, Persian Gulf War Veterans Act of 1998, Veterans' Benefits Act of 2010). She stated that the Veterans' Benefits Act of 2010 is what really expanded the legislature to include post-9/11 conflict veterans because it called for a review of chronic multi-symptom illness (CMI).

She gave a list of exposure agents in the GW Legislation that the IOM and the National Academy of Sciences were requested to study (33 in total). The list included organophosphate pesticides, carbamate pesticides, PB pills, chlorinated hydrocarbons, low-level nerve agents like sarin, synthetic chemical compounds, sources of radiation, environmental particulates and pollutants such as oil fire byproducts and sand micro-particles, diseases endemic to the region, as well as time compressed administration of multiple live, "attenuated," and toxoid vaccines.

Ms. Wedge explained that each IOM study has a specific statement or task. Also, she stated that the IOM committees have determined an association between exposure to the agents listed in the legislation and long-term adverse health effects in more than 10 volumes. She drew attention to Volume 4 (2006), which looked at the health effects of veterans deployed in the GW compared to veterans not deployed to the Gulf War. She discussed additional study requests from the legislation which included determining the long-term adverse health effects associated with sarin (2004) and depleted uranium (DU) (2008), ALS in veterans (2006), treatment of Chronic Multisymptom Illness (GWI) (2013), and a Case Definition of Chronic Multisymptom Illness (GWI) (2014). The last study on the case definition resulted in the IOM stressing that the VA use the term "Gulf War Illness" to describe the chronic health symptoms encountered by Gulf War veterans.

She noted that the IOM committees had not been asked to determine whether a unique Gulf War syndrome exists or to make judgments regarding the veterans' levels of exposure to putative agents. They also had not been asked to focus on broader issues, such as the potential costs of compensation for veterans or policy regarding such compensation.

She briefly outlined the IOM study process so that the Research Advisory Committee would understand what the IOM can and can't do given the committee process (this is for all IOM studies, not just GWI studies). She began by outlining the selection of prospective members, whom are chosen on the basis of knowledge and experience. There are certain steps that take place before appointments are finalized to ensure that every attempt is made to have a balanced committee with a commitment to review the evidence with an open mind. Next, she discussed committee deliberations and how these are made, and finally, detailed the role of the sponsor. The sponsor can (1) provide suggestions for nominees for the committee, which are considered along with suggestions from other sources; (2) address the committee during an open session, typically at the first meeting, to articulate their perspective on the charge to the committee; and (3) provide information, through the IOM staff (that is, the sponsor has no direct contact with committee members), to the committee as requested by the committee. The final part of the study process is the report review and release.

She detailed the committee's approach to completing a report review. The IOM reviews all peer-reviewed published literature with human epidemiologic studies having more weight than animal studies. All studies are reviewed by the entire committee to reach a consensus on whether a study is key or very supporting.

She stated that there are five different categories of association used in determining the strength of evidence, ranging from limited/suggested evidence of no association to sufficient evidence of a causal relationship. She detailed the description of each category and what it implies about the research. She used findings from Gulf War Reports Volumes 1, 2, 3, 6, 8, and 9 as examples to highlight "sufficient evidence of a causal relationship." These included benzene and acute leukemia and aplastic anemia, sarin and a dose-dependent acute cholinergic syndrome, blast injuries and penetrating eye injuries and some long-term effects on a genitourinary organ, and deployment to the Gulf War and Post-Traumatic Stress Disorder (PTSD). There are other findings from Gulf War Reports suggesting sufficient evidence of an association for various exposures and resulting conditions.

Her recommendations for future research were to implement well-designed follow-up studies of robust GW cohorts to track mortality; cancer (particularly brain cancer); neurologic and psychiatric outcomes, such as ALS and multiple sclerosis conditions; and other health conditions that occur later in life such as cardiovascular disease, other cancers, and neurodegenerative diseases. Also, she recommended furthering the study of functional gastrointestinal disorders. Lastly, she identified the need for large studies to identify genetic variants and rare environmental events related to outcomes. The committee determined that investigations based solely on self-report were unlikely to provide more information on GWI and would not be the most helpful going forward. Instead, Ms. Wedge said that the IOM thinks thought there needed to be more rigorous studies to identify biomarkers of GWI using genetics, molecular diagnostics, and imaging. She acknowledged that these were likely to help with diagnosis and treatment, even if they were unlikely to identify the cause.

Dr. Ralph Loren Erickson, GW veteran and acting Chief Consultant for Post-Deployment Medicine, underscored some of the points that Ms. Wedge had made in order to highlight the importance of the IOM dealings. First, he stated that the IOM does not make recommendations or presumptions to the VA. Second, he underscored the independence of the National Academy of Sciences and the IOM. He also stated that once the VA makes a charge to the committee, they do not interfere with the committee, but stay "hands off."

Dr. Golomb commented regarding Ms. Wedge's remarks about future recommendations, saying that while she acknowledged that many on the Committee agree that they should be focusing on biomarkers, biomarkers in the absence of connecting them to the health concerns of GW veterans don't have much utility, so she would urge not discounting the reports of GW veterans or implying that they do not have an important place in this research agenda. Dr. Golomb also acknowledged the importance of these early reports in directing the initial research to get to where they stood thus far. Ms. Wedge agreed but stated that we need to build more on the foundation.

Dr. Sullivan asked a question regarding the classification of association classes. She asked at what threshold level does research suddenly become a connection, given that there is so much data and there are so many studies out there. Ms. Wedge replied that their interpretation is much more qualitative, so studies are not weighted equally. Dr. Sullivan replied that not many investigators were doing this type of research, so if there were just a few definitive papers published, they should not be ignored and should be counted for consideration as sufficient evidence in IOM reports.

Dr. Klimas remarked on her prior experiences sitting on committees and thanked Ms. Wedge for her perseverance.

Jim Bunker commented on the number of studies that look for causal relationships between a certain exposure and the related health problem, but he identified the complexity of the issue by stating that many veterans had exposure to multiple agents and yet there hadn't been any study that looked at a combination of all 33 identified agents. He stated that the most he'd ever seen had been a combination of three agents. He strongly suggested that a rigorous scientific study be conducted with exposure to all 33 agents.

Dr. Hauser commented that the list of things that the committee believes are not related to deployment is very small. He noted that the IOM had in fact acknowledged that a multi-symptom illness is associated with deployment. He summarized Mr. Bunker's comment by saying that Mr. Bunker believed that more science needed to be done before we would truly know what's going on in GW veterans.

**Update of VA OPH Gulf War Research**
**Dr. Victor Kalasinsky**

Please refer to **Appendix A – Presentation 5** for Dr. Kalasinsky's presentation. Dr. Kalasinsky oversees the Gulf War research portfolio at the VA Office of Research and Development (ORD). He provided the VA ORD mission statement and vision, including the number of VA Medical Centers and their Research and Development (R&D) funded projects. He showed a graphic of the Veterans Health Administration ORD overseeing four different research services (Biomedical Laboratory R&D, Clinical Science R&D, Health Services R&D, and Rehabilitation R&D).

Dr. Kalasinsky provided an outline of the type of research involved in each branch. This includes investigator-initiated research (clinician researchers) which covers pilot projects, merit review, clinical trials, and career development awards. There is also service-directed research and a cooperative studies program (CSP). He noted that there is public access to information regarding VA/ORD funded research. Refer to **Appendix A – Document 1** for the projected FY2014 ORD support for ongoing Gulf War research projects.

He provided another overview of the VA ORD application process stating that the ORD invites VA intramural researchers to submit proposals for Gulf War research using the mechanism of "Requests for Applications" (RFAs). Dr. Kalasinsky said that since 2011, these RFAs have been issued by the ORD twice per year on a consistent basis. He stated that the VA/ORD has a

specific merit review panel with expertise in Gulf War issues to insure high quality, independent, and unbiased reviews of Gulf War research proposals submitted to the ORD.

He showed a slide of how the ORD selects GW research projects for funding. He explained that review panel scores are a major determinant in who receives funding, but that the ORD can pick projects out of order when needed to address key priorities and balance the portfolio. He provided examples of Gulf War research RFAs which fell under three categories: Biomedical Laboratory Research & Development (BLR&D), Clinical Science Research & Development (CSR&D), and Health Services Research & Development (HSR&D).

He stated that there are three advisory committees that give input to the Gulf War Research program. These are the National Research Advisory Council (NRAC), the Research Advisory Committee on Gulf War Veterans' Illnesses (RAC-GWVI), and the Genomic Medicine Program Advisory Committee (GMPAC). Dr. Kalasinsky explained that the VA ORD operates according to a strategic plan that they had developed for the Gulf War. He outlined the specific Gulf War Research Strategic Plan (2013-2017). This can be found online at: http://www.research.va.gov/resources/pubs/docs/GWResearch-StrategicPlan.pdf. This plan resulted as a recommendation and with input from the Research Advisory Committee on Gulf War Veterans' Illnesses. He stated that it was subject to future updates as needed.

He detailed the VA ORD Gulf War Research Funding from 2004-2014 to provide an idea of the funding for each fiscal year. The fiscal year total for 2004-2014 was $134.5 million.

He then delivered a listing of the Gulf War research projects that were active in 2015 (24 total) focusing on treatment, mechanistic diagnostics, and other research areas. He also listed the GW research projects that had been selected for funding but hadn't started yet. Finally, he listed recently completed Gulf War research projects. Refer to **Appendix A – Document 2** for the clinical trials funded by the DoD Congressionally Directed Medical Research Programs' Gulf War Illness Research Program.

Dr. Kalasinsky then discussed the VA ORD's role in the IOM reports. In the "Chronic Multisymptom Illness in Gulf War Veterans: Case Definitions Reexamined" report, the IOM made three recommendations. The first was that the Department of Veterans' Affairs use the Center for Disease Control and Prevention and Kansas definitions for Gulf War Illness because they capture the most commonly reported symptoms. The VA concurred, and this is now in practice. The second recommendation was that the Department of Veterans' Affairs, to the extent possible, systematically assesses existing data to identify additional features of chronic multisymptom illness, such as onset, duration, severity, frequency of symptoms, and exclusionary criteria to produce a more robust case definition. The VA concurred, and was currently in the process of putting that recommendation into practice. The third recommendation from the IOM was that the Department of Veterans' Affairs use the term *Gulf War Illness* rather than *chronic multisymptom illness.* The VA concurred in principle, and had decided to put into practice the use of the term "Gulf War Illness presenting as chronic multisymptom illness." Dr. Kalasinsky stated that this was because if a patient came in with symptoms of Gulf War Illness, there is no clinical practice guideline for this, yet there is a clinical practice guideline for chronic multisymptom illness, which is the guideline that had been used for years to treat Gulf War

veterans.

Dr. Golomb commented that the definition of CMI encompasses anything from vitamin D deficiency to undiagnosed hypothyroid conditions, conditions with very different treatments. She suggested coming up with treatment guidelines for Gulf War Illness, rather than forcing it into a broader category that encompasses many different conditions with different presentations, causes, and treatments. Dr. Kalasinsky responded by saying that they simply had trouble identifying all of the symptoms of Gulf War Illness. Dr. O'Leary responded as well and said that this recommendation was specifically pertinent to research, but also that there is a certain amount of bureaucracy when taking things from research and applying them to clinical findings and that doing so is not instantaneous. However, he said that whichever way the department chose to respond, they would "get all the pieces together" so that no veteran fell through the cracks.

Dr. Golomb asserted that the IOM made the recommendation to use that terminology for a reason and stated on behalf of the RAC that she believed all Committee members would agree with that reason. She understood that the VA wanted treatment to follow a recognized term, but in her opinion, they could just recognize Gulf War Illness as its own recognized term. Her concern was for veterans who meet the CDC or Kansas definition of Gulf War Illness, but do not have a symptom listed under the umbrella term "chronic multisymptom illness" and thus are being denied disability. She declared that the failure to call it "Gulf War Illness" would have repercussions in the administrative, clinical, and research settings.

Mr. Bunker responded to Dr. Golomb's comments, saying that although at the time there were no disability benefits guidelines, there would be one coming out which would help veterans with GWI or undiagnosed illness. He stated that he had met last month with the Undersecretary of Benefits, who said that there would be a Disability Benefits Questionnaire (DBQ) form coming out shortly for those with undiagnosed illness or GWI for that portion of the claim. This would address that current obstacle of lack of disability benefit guidelines.

Dr. Kalasinsky continued, stating that there were two other ongoing IOM reports (Gulf War and Health, Volume 10: Update of Health Effects of Serving in the Gulf War, and Design of an Epidemiologic Study for MS and Other Neurologic Disorders in Pre- and Post-9/11 Gulf War Veterans). Dr. Hauser commented on the usefulness of looking at something like MS, and asked Dr. Kalasinsky whether that study still planned on using combined health care data sets from multiple different sources. Dr. Kalasinsky confirmed that it would.

Dr. Kalasinsky mentioned the two GW research biorepositories [CSP #585 Gulf War Era Cohort and Serum Biorepository and the Gulf War Veterans' Illnesses Biorepository]. More information on these biorepositories can be found at the following link: http://www.research.va.gov/programs/tissue_banking/gwvib/default.cfm.

Dr. Kalasinsky concluded by giving an overview of the VA-DOD coordination relating to Gulf War research.

Dr. Klimas made another point concerning the discussion over the use of the term "Gulf War Illness." She stated that as a Research Advisory Committee, the Committee is supposed to advise

research, which doesn't actually have a direct effect on health care (although she hoped that their work one day would). So stated that how the term is used within the RAC and research community wouldn't affect the patients' clinical care guidelines. Dr. Kalasinsky responded that the ORD is part of the VA, so whatever the VA uses is the official word. He stated that keeping the same terminology keeps consistency. Dr. Klimas also mentioned that her own group had previously been using the Fukuda case definition, but that the Kansas criteria is a stronger case definition so she advised that a conversation be held about that. Dr. Kalasinsky said that it was possible to use both within a given data set. However, Dr. Golomb said that the Kansas criteria unequivocally show higher specificity.

Dr. Golomb also asked a question regarding the presentation slide that discussed funding, concerning the decision-making process about which studies are funded. She asked whether the VA would consider forming a formal veteran relevancy review panel within the VA that could partake in the review panel on decisions regarding funding projects. The panel would review proposed studies to ensure that they were meeting the concerns of that group. She claimed that her suggestion would ensure that the approach that the VA was using was really funding the right research. She also mentioned that the panel could review projects that the VA denied but were funded by the DOD, and see whether the results of such studies were found to be significant. For the sake of time, the current discussion was tabled. However, Dr. Sullivan noted that in the meeting binders, there were copies of the funding portfolio from the VA and a summary of DOD funding that could be reviewed.

Dr. Sullivan requested that Dr. Kalasinsky send the Committee the Strategic Planning as soon as possible for review by the Committee, as well to share the new RFAs with the Committee.

**Million Veteran Program and GW Illness Research**
**Dr. Timothy O'Leary**

Dr. Sullivan introduced the final speaker for the day, Dr. Timothy O'Leary, Chief Research and Development officer. Please refer to **Appendix A – Presentation 6** for Dr. O'Leary's presentation slides. Dr. O'Leary discussed some of the highlights of the Million Veteran Program (MVP) as well as how it pertains to GW research.

He discussed how the MVP is organized and noted the broad range of consent that GW recruited patients give. He stated that veterans' electronic health record can be accessed and merged with MVP data and that this is then turned into a phenotype or case definition. There were almost 370,000 subjects enrolled in the MVP study. He anticipated they would reach 400,000 subjects enrolled by June/July and expected about 50,000 of those to be GW veterans and additionally expected half of those veterans to have been deployed in the theatre.

He discussed the "chip-based analysis" (using an exome chip) as well as its high-power capabilities and limitations. For example, it can detect single nucleotide polymorphisms (SNPs) in the BChE gene. About 250 SNPs had been identified.

Dr. O'Leary talked about the questionnaires to be used in the study and their limitations. He was hoping to have 7,500 GWI patients in the study. He stated that they were developing exclusion

criteria mapping back to the public health record. The MVP study had four coordinating centers. He discussed each and what their role was. He then took a quick break for questions.

Dr. Crawford asked whether there was a mechanism to re-contact veterans that reported GWI symptoms to obtain blood samples from them, collected in a manner that would be consistent with the protocol to do proper analyses. Dr. O'Leary said they could consider designing a study to make this feasible and that this was a great topic for future discussions. Dr. O'Leary also stated that the MVP was intended to be an ongoing epidemiological cohort for genomics as well as other focuses.

Dr. Klimas asked a question about the study timeline. Specifically, she asked when Dr. O'Leary thought his goals might realistically be accomplished. Dr. O'Leary responded, saying that a scientific review would occur on June 4th. Also, that they would begin to see activity beginning around FY2016 and it would be FY2017 before any real analysis got done.

Dr. Sullivan asked if Dr. Provenzale's group would be leading this study. Dr. O'Leary stated that Dr. Provenzale would be involved, but that the planning committee was quite broad. Statistical geneticists from Yale and Duke would also be involved. He also noted that the committee members could change over time and that this was meant to be executed as a cooperative studies program. Dr. Sullivan commented on how having this sample size was a tremendous opportunity. She also asked if the SNPs would be analyzed for inflammatory biomarkers, cytokines, and other things of that nature, and Dr. O'Leary confirmed that it would. He said that the initial pass would use standard techniques, but then they could look back and do more complex analyses in regions of interest.

Dr. Hauser asked about the timeline of the genotyping. Dr. O'Leary expected that this would be completed within two months of reaching the 400,000 subject target number. He also noted that in his opinion, the rate-limiting part of the study would be deciphering who has GWI based on the surveys and case definitions.

**Public Comment**

Dr. Hauser began the public comments by thanking everyone who came and stayed for the day.

Joanne Lemieux explained that she is a GW veteran and the widow of a GW veteran. She said that it was an honor to see the work that the Committee had been doing. She said that her husband died of colon cancer and then she discussed the health problems of many that were in her unit such as cancer, kidney problems, and cardiac problems. She said that she suffers from many of the illnesses that are considered "undiagnosed" including chronic pain. She commented that she is interested in the work that was currently being done and was interested in seeing how the Committee and researchers would proceed.

James Pepple spoke next for public comment. He spent thirty-two years in the United States Army. He said that he spent a lot of time in the Gulf War, and iterated how in the Gulf War, there were many exposures. He also commented that in his opinion, research should focus on a combination of exposures rather than one exposure and its effects. He ended by commending the

Committee for the work they were doing.

Dean Lundholm spoke for public comment. He mentioned how a trigger as seemingly harmless as mothballs could be detrimental to a veteran with multiple chemical sensitivity after being exposed to so many chemicals. He then commented on how the VA had recommended a "detox" as treatment, yet had not provided detox services. He said that, for example, a twenty-eight day detox from everyday exposures was recommended. He stated that the VA should be compensating veterans for available treatments, such as coenzyme Q10 or a detox program. He also said that twenty-five years later, it is still an issue that veterans are not receiving compensation due to not meeting definitions of the illness.

Kevin Fearon spoke for public comment. Kevin came to the conclusion that the protocol seemed flawed. He said that different VA facilities had different protocols for diagnosing, testing, or even getting the veteran onto a list if they were a GW veteran. He said that he felt like he was being pigeon-holed, becoming stuck and then unable to go elsewhere.

Michael Bann spoke for public comment. He stated that he is a GW veteran and said that it was frustrating that records had just seemed to disappear and that still nothing had been done to improve the veterans' health. He said that he simply wanted his health back.

Paul Johnston spoke for public comment. He stated that his unit was scattered all over the battlefield during the Gulf War. They captured enemy equipment that would damage the United States and he noted that this was covered with radioactive material (DU) or chemical weapons. He said that everyone in his unit got sick in different degrees. They all have multiple chemical sensitivity and most have a lot of breathing problems. He described his frustration that the VA does not see veterans as a group (even if they have the same doctors, he said they are seen separately) which made it seem like the VA wants to make sure the veterans are not in contact. He also said that the VA doctors don't write down what veterans tell them about their illnesses or keep accurate files about their symptoms and illnesses. The veterans are told that their symptoms are not within the diagram of what they can be treated for. He said it was disgusting to have to beg to be treated and to have to fight through bureaucracy to get what was needed in order to stay alive. He also mentioned that he got sick when he was over in the Gulf, not when he got back, and that a lot of veterans did get sick over there. He said he was frustrated about the lack of medical records and suggested keeping accurate records and real data which would help in their treatment. He also mentioned that he was unaware about the RAC meetings until a month prior, and then he informed his unit, all of whom are sick on different levels. He insisted that all the veterans are asking for is honest medical care and to be seen by a doctor that really cares about treating them. He said that he would gladly serve again, but as long as there was promise that sick veterans would get treated. He pleaded that the Committee do the best they can to find a cure for GWI.

Jennifer Plotts spoke for public comment. She served in the United States Navy and stated that she was bothered by the VA not wanting to use the terminology "Gulf War Illness" anymore. She also noted that while Operation Desert Shield/Desert Storm was in 1990-1991, we were still currently in the Gulf War according to the VA. She explained the many health problems of her ex-husband. She said that she went to serve in the Gulf War in 1993 and that she now has Gulf

War Illness. She said that she is very sick for her age and was worried about receiving treatment and becoming healthy again. She also said that her second husband was getting sick now that it had been ten years that they'd been together. She asked the Committee to be more forceful and expand their research to get her into studies because she's a suffering GW veteran and needs help.

Steve Hohman spoke for public comment. He mentioned that he recently came out of a DOD study. He said that it was his hope that this board would continue to delve into positive research. He welcomed the new board members and veterans. He also said that he hoped there was no tension between GW veterans and the VA, and he hoped the VA would come forward in a timely manner with information on how to treat GW veterans, which would eliminate the distrust between veterans and the VA. He asked the VA to ensure every Desert Storm veteran represented at the hospital that registered them attend this meeting or watch it once it went to live stream. He suggested hanging a poster at the VA or a VA hospital asking "Have you registered for the GW registry? Do you know about the WRIISCs? Do you know about the RAC and the current research?" He suggested this because he'd met veterans that still were unaware about the RAC, the current research going on, and the WRIISCs, and this would be a simple and inexpensive solution. He concluded by recognizing the names of eight fellow veterans who had passed away.

Michael Rupert spoke for public comment. He appreciated that Secretary McDonald attended the meeting. He also commented on the length of time that it had been since the Gulf War and stressed that it could not be another twenty-five years until there were treatments. He commended the work of the researchers on the Committee and had a positive outlook.

Albert Donnay spoke for public comment. He is a toxicologist and environmental health engineer. He passed out the testimony he delivered in 2003, which can be found in **Appendix C – Document 1**. He stated that his testimony in 2003 deserved repeating. Then, he had encouraged the VA to examine MCS and he noted that there were twelve abstracts attached to his testimony, yet it seemed like the research on MCS suddenly stopped, which he said was unfortunate because it's the most prevalent diagnosis in any GW veteran. He welcomed the discussion of MCS and urged the Committee to ask VA to include MCS in their clinical guidelines for diagnosing it because it was still not listed so veterans could not get a diagnosis. He also said that he was still concerned with carbon monoxide (CO) exposures, which was also included in his previous testimony in 2003. He stated that CO is a cumulative poison that accumulates in the tissue as our bodies produce it or are exposed to it. He mentioned that despite this, it did not make the IOM list of GW agents and it remained to be studied. Thus, he studied it himself for his doctoral dissertation and found that (1) There is no biomarker for chronic CO poisoning, but that there is a simple way to collect arterial, venous, and tissue samples, and these samples have shown that CO needs to be tested at the level of tissues, not blood; and (2) CO poisoning treatment is simple and that four months of daily home oxygen therapy or breathing methods can overturn all of the CO heme and restore a normal level of CO in arteries, veins, and tissues. He stated that this would not only help with the chemical sensitivity that veterans experience, but also their multi-sensory sensitivity such as sensitivity to light, temperature, and touch, all of which CO modulates. He invited veterans that could not get help from the VA to contact him. He stated that he does not charge for his services to veterans.

Michael Jarrod spoke for public comment. He suggested that researchers look into volume loss in the cerebellum, after describing his own experience at the WRIISC and the results of his MRIs. He said that he thought it was an important component that was being overlooked.

Tracie Johnston spoke for public comment. She questioned how the VA could possibly link self-identified veterans with GWI to their medical records if the VA says the medical records no longer exist. She also noted how the war didn't really end in 1991, but that her husband kept going back there until 2000, just before 9/11. She questioned why studies do not examine multiple exposure combinations.

Glenn Stewart spoke for public comment. Mr. Stewart thanked Dr. Steele, Dr. Klimas, and everyone else on the Committee for not giving up on the veterans. He had questions regarding the brain bank and the spine samples. He was wondering whether anybody oversees that, ensuring the data is being collected correctly and not being discarded. The Committee confirmed that there were specific regulations and specified the two brain banks, which are for ALS and GWI. The committee explained that the tissue would be shared with researchers that propose research to VA. Mr. Stewart also suggested that the term "CMI" (chronic multi-symptom illness) no longer be used. He said that this was because unless a veteran has a specific neurological ailment, the claim would be denied. He wanted to have a legitimate "name tag" in order to submit a claim successfully.

Angela McLamb spoke for public comment. She is a GW veteran that was deployed there shortly after the Khamisiyah demolitions. She stated that she was there on behalf of GW veterans, their spouses/partners, their children, and anyone else they had close contact with, as well as the Gulf War veterans that had died due to their service to our country. She wanted to follow up on the status of the 1990's VA research on ill GW veterans, their spouses, and their children. She said that last year, she was told it was not located, so she wanted to know whether those results had been located. She also questioned whether anything was being done to communicate and follow up with those that had completed the research. She recommended a registry be started and that this information be written in veterans' medical records. She also recommended a law to be written for veterans to be seen at the VA for those conditions. In her opinion, there are too many GW veterans with medical problems that they must be service-connected. She also stated that she completed the Persian Gulf War registry, but was later notified that the original one she went to closed down and a different one had started. Thus, she stated that there needed to be better communication about the registries so she could know whether it was true that the first one shut down and also know whether she needed to come in and have another done. Finally, she commented on the anthrax vaccine, saying that she was told it was FDA approved and not related to GWI. However, later she said she was told that it was not FDA approved but that they still had to take it. After returning from the war, she read an article in the *Army Times* that said that the United States had eventually ran out of the anthrax vaccine, so additional vaccines were sent from Japan. She questioned whether this vaccine was approved in Japan and if they had the same approval standards as in the United States. She also questioned whether anyone had done any research into what exactly the vaccine was that Japan gave them.

Dr. Hauser advised Ms. McLamb to write down these questions and send them to the Committee.

On behalf of the Committee, Dr. Hauser noted that the last forty-five minutes were the highlight of the meeting. He said that the public comments made it an issue of the people instead of an issue of science. He stated that the remainder of public comments would continue at tomorrow's session.

**DAY 2**

**Ethics and Federal Advisory Committee Training**
**Ms. Purnima Boominathan**

Please refer to **Appendix B – Presentation 1** for Ms. Boominathan's presentation slides. Ms. Boominathan began by stating that ethics training was a requirement, but was also an opportunity for questions and comments. She explained who a "special government employee (SGE)" is; that is, who that designation encompasses. She provided the Office of General Counsel's Ethics Specialty Team information and encouraged that they are contacted if a special government employee ever finds a problem or needs advice. She explained the importance of seeking ethical advice. She explained when the rules of ethics apply, and then transitioned to talk about the categories of ethics laws. She explained the definition of a "conflict of interest," which is that it is a crime for one to participate personally and substantially as a Government officer or employee in a particular matter which would directly and predictably affect one's financial interest or a financial interest imputed to that person. She touched on the exceptions to conflicts of interest for SGEs, such as individual waivers (in writing) or multi-campus exceptions.

She clarified prohibited compensation and also listed restrictions on "switching sides," working for parties opposing their agency. The standards of conduct boil down to two basic principles: (1) do not use your public office for private gain and (2) do not give unauthorized preferential treatment to any private organization or individual. She then detailed what misuse of the position would entail.

Dr. O'Leary had a comment in regards to the aspect of "side switching" which was that a SGE may not serve as an expert for a party opposing their own agency where they serve on a committee established by statute or serve on the committee for more than sixty days. He noted that the RAC was established by statute. Ms. Boominathan acknowledged that indeed the RAC was established by statute and stated that therefore it is true that a member on the RAC cannot serve opposing VA. She said that if something ever came up where one should serve as an expert witness against VA, he or she should contact the Ethics Specialty Team because they served on this Committee.

Dr. Sullivan then asked how this applied to congressional testimonies. Ms. Boominathan responded that congressional testimony is always permitted in your personal identity, meaning that there is no problem to testify as an individual on the Hill, but one is not supposed to testify on behalf of this Committee on the Hill unless the Ethics Specialty Team specifically permits it. She again clarified that as an individual there is no problem in testifying.

She discussed the regulations (and exceptions) surrounding teaching, speaking, and writing as a

SGE. For example, if a member were asked to speak at a conference about this Committee, she said that the Ethics Specialty Team should be contacted so that the content of the lecture could be approved. She next discussed the rules surrounding gifts, which is that a SGE may not accept a gift given because of his or her official position or from a "prohibited source." She listed prohibited sources and explained the minor exceptions. She discussed the rules surrounding charitable fundraising as well as other laws and regulations (Emoluments clause, foreign gifts and decorations act, and foreign agents). Lastly, she described the Hatch Act, which restricts certain political activities of government employees.

She concluded the presentation and took questions.

Before continuing, Dr. Hauser noted that forming clear, concise, actionable recommendations was the charge given to the Committee, and that he wanted that to be the focus for the year. Due to not having a lot of time before September, he also suggested these recommendations be given in the form of something like a memo rather than a large volume. He stressed identifying the "low-hanging fruit" that could make a difference if it was prioritized and given the support of the VA system. He also noted how the Committee is supposed to have three meetings per year. He mentioned that the Committee is scheduled to meet June 23, 2015 and then again on September 29, 2015.

Dr. Klimas stated that she wanted substantial time for the Committee to discuss, more than the one hour typically scheduled at the RAC meetings. In her opinion, the Committee's focus for discussion should be the combination of the VA and DOD research portfolio. She said that the focus of next meeting should be a real in-depth understanding of where the science was currently funded, what the barriers might be, and how to push it forward. She wanted to respond to the comments of the veteran community, which was that researchers should be focusing on translational research and clinical trials; that is, bridging the gap between the research side and the clinical side by applying the findings from the literature and translating them into clinical care guidelines. She suggested having a discussion that included leadership from the clinical care side. For example, she said that the RAC could potentially have a combined session with the clinician's committee. Dr. Hauser agreed on perhaps focusing the next two meetings on clinical research and imaging, because yesterday's meeting was so heavily focused on genetics, animal models, and biomarkers.

Dr. Klimas also mentioned that she did not want to spend all the discussion time reviewing specific individuals' projects, but would rather have broad looks at the projects, looking at the current state of science and sticking to overviews of the VA and DOD portfolios, noting the strong and weak points of the portfolios in order to give rational advice. Then, she said that the Committee could have discussions with their leadership regarding future plans. She suggested that someone from the integration panel come and talk about DOD leadership, including where they stood currently and what the intention was down the line three to five years from that time. Dr. Hauser asked whether the Committee had the time and/or capability to go over these portfolios in that way, and Dr. Sullivan said that they did. Dr. Hauser suggested taking the VA's update report and turning it into a three-page document. He reaffirmed that the goal in 2015 would be to come up with clear, concise, actionable recommendations that could be concretely recommended going forward.

Dr. Hauser and Dr. Sullivan discussed the format of the next meeting, including whether or not there should be less scientific presentations and more portfolio discussions instead. Dr. Crawford suggested focusing on one specific area, for example biomarkers, and sitting down and discussing the current content of the portfolio and the direction it needed to go in. Dr. Hauser suggested having Dr. Sullivan assign the Committee members with a topic as opposed to bringing in additional outside speakers. However, Dr. Sullivan also noted how at that point in time and going forward, the Committee could talk about the broader picture, but that this was only because they have had meetings such as this where the Committee members could get the background on the science, animal models, and recent findings.

Dr. Hauser transitioned back to the discussion topic of how the Committee would focus on translating clinical research findings into clinical care, despite the fact that the Committee is not charged with clinical care. Dr. Golomb commented, saying that many veterans were frustrated because their physicians were not familiar with Gulf War Illness. She said that the training for GWI was in the era before there was a lot of supporting evidence for it, so suggested a training that would bring physicians up-to-date on current research. She thought that this would also make the physicians more sympathetic to current veterans, as many initially considered it malingering or psychosomatic in nature. Dr. Sullivan commented by saying that what the RAC was hearing was that this was no longer the attitude of most primary care physicians and that the physicians do care but don't know much about GWI. Dr. Sullivan did agree that education is key and that it would still be important to disseminate the findings of this research and the work of the RAC to primary care providers.

Dr. Klimas quickly commented that there are avenues for training every VA physician for veteran-specific issues. She mentioned that there was no required GWI training like there is for PTSD and suicide prevention, but also said that it would be up to the clinical committee to create and arrange such training.

Dr. Scott Young commented and said that in the recommendations, the Committee should be very specific about the speed and timing of when things should happen, seeing as it was twenty-five years after the Gulf War. He also said that physicians use all kinds of data when they create their clinical processes pathways and therefore being very specific in whether the data is traditional or not in the recommendation could be helpful. Dr. Hauser noted how the RAC is in fact a *Research* Advisory Committee, but if the Committee could make recommendations that translate the research so that it influences clinical care, it would be very impactful.

Mr. Bunker commented on some of the problems the veterans experience inside and outside of the VA. These problems included the fact that some doctors do not believe in the syndromes, which he thought was still a problem that needed to be overcome despite the fact that the VA had updated the guide on how to care for Gulf War veterans. He also suggested (and hoped it would be a recommendation by the Committee) that a study examine the same patients now, twenty years later, that it had examined previously; that is, draw their blood, see how their health has changed in the last twenty years, and look for biomarkers in all of them now.

**Update of VA ORD Gulf War Research Portfolio**
**Dr. Robert Bossarte**

Dr. Sullivan announced that the Committee had asked the researchers of the VA Office of Public Health (OPH) to give the Committee an update on the Gulf War research program. She then introduced Dr. Robert Bossarte, director of the epidemiology program in the Office of Public Health, and Dr. Erin Dursa, a health scientist in the post-deployment neurology program.

Dr. Bossarte presented first. For his presentation slides, please see **Appendix B – Presentation 2.** He gave a brief overview of his agenda. He then defined and explained the data model and addressed the limitation such as the sample size, which the OPH tries to resolve by predicting error outcomes so that the necessary sample size can be estimated. He mentioned that the other limitation when using a survey approach is the number of questions that can be asked, due to fatigue of the person taking the survey. He discussed where different data, such as mortality data, was obtained. Dr. Sullivan asked if he used state registries. He responded that while state registries were in fact useful for things like tumor data, he was obtaining mortality data from the CDC.

The Epidemiology Program conducts public health surveillance and research on period-specific veteran cohorts. He described the components of this program. He then stated that the VA OPH had done three survey studies and displayed them on a timeline (1995-1997, 2003-2005, and 2012-2013). He mentioned that to date, the survey data had been represented as cross-sectional but that they were working to develop a longitudinal data file in order to consider changes over time. The first study took place in 1995-1997 and was the first large scale study of Gulf War and Gulf War-Era veterans following the 1991 war. He next described the details of this national health survey of Persian Gulf War veterans. The sample was 15,000 GW veterans (deployed) and 15,000 Gulf War-Era veterans (non-deployed) which he broke down into further detail. He also noted that the Gulf War-Era veterans were sampled from 50% of the total known non-deployed veterans during that time period. He described an overview of the type of questions the survey contained (that is, what aspect of health it related to). The study found that overall, Gulf War veterans reported higher prevalence of functional impairment, healthcare utilization, wide variety of symptoms, serious chronic health conditions, lower perception of general health, miscarriage (female veterans and female partners of male veterans), and birth defects among live-born infants (female veterans and female partners of male veterans).

The second series of studies took place between 2003 and 2005. This was the first follow-up of the panel of Gulf War and Gulf War-Era veterans contacted in 1995. He again described the topics the survey contained. The results of this study were published by *Kang et al, 2009 (JOEM)* and demonstrated that fourteen years after deployment, Gulf War veterans continued to report significantly higher rates of many adverse health outcomes compared with Gulf War-Era veterans.

The third study took place between 2012 and 2013 and now included web-based participation in the survey as well. This follow-up study included questions on a greater number of health outcomes, for example Amyotrophic Lateral Sclerosis (ALS). The results of this study were not yet published, but indicated that Gulf War veterans still continued to report significantly higher

prevalence of many adverse health conditions.

He next described the Gulf War Veteran Roster, a computerized data file of 621,901 Operation Desert Shield and Operation Desert Storm Veterans deployed to the Kuwaiti Theater of Operations in 1990-1991, and a computerized data file of 746,247 non-deployed veterans that served as the comparison population who served during the same period. These files comprised various data elements.

Dr. Sullivan pointed out that at a prior meeting, she noted that the 621,901 does not capture all GW veterans that were there at the time, and that it could be problematic if deployed Gulf War veterans are included in the other group (the 746,247 non-deployed veterans). Dr. Bossarte confirmed that this could be the case, as some veterans in the 'non-deployed' group could have been deployed later on. Dr. Sullivan said that this was extremely problematic. Dr. Bossarte said that they were examining this grouping.

Dr. Sullivan recommended that the VA also re-examine their groupings particularly in regards to sarin exposure, due to recent observations and corresponding concerns she raised. She suggested that they consider regrouping some of the data, which Dr. Bossarte replied that they were currently doing.

Administrative data provide a mechanism for assessing the prevalence and incidence of diagnoses and service utilization among veterans who use Veterans' Health Administration (VHA) services. He stated that when certain characteristics of GW veterans and GW veterans who used VHA services (such as gender, ethnicity, age, birth year, branch of the military, and enlistment) where examined and compared, the GW veterans who had utilized VHA services had very similar patterns to the overall GW veteran group.

He also displayed a graph depicting the prevalence of diagnoses (of ICD-9 diagnostic categories among GW and GW-Era veterans and with history of VHA service use, FY2002-2013). These data too, were roughly similar, and if there were any differences in a particular diagnosis, then this gave the VA the opportunity to research this in further detail.

He next presented his mortality data among Gulf War veterans. The top five causes of mortality in 2011 were the same between deployed and non-deployed Gulf War veterans. He then showed data comparing the causes of death of deployed and non-deployed Gulf War veterans to the United States general population at that time point in 2011. Dr. Golomb noted that civilians are excluded from the military for health conditions and that among the military, certain health conditions exclude some for deployment, so she wondered if analyses had been done that compare deployed versus non-deployed Gulf War veterans that control for prior health problems. He said at that point in time they had not done such an analysis. He said they did not have the medical history before service and that even their access to DOD military records was a bit limited. Most of the analyses they had at that point were cut in time (although he realized there were recommendations for that to change) or were health factors acquired from VHA records. Dr. Sullivan commented that it would be helpful if they completed the regrouping she suggested (updating deployed versus non-deployed) and then conducted the mortality analyses, including relative risk for select causes of death among GW veterans.

Dr. Bossarte then presented oil well fire smoke and nerve gas at Khamisiyah exposures among Army Gulf War veterans as an example of linking one data set to another to begin to acquire information from that data set. He discussed VHA service use by exposure group (oil well fire exposure, Khamisiyah exposure, or both) and by fiscal year. He also presented the top diagnoses or procedures at the first visit by exposure group and fiscal year (2000-2014).

The last thing he mentioned was a study in Khamisiyah exposed veterans. He noted that they would be using both the Kansas and CDC definitions of GW illness in the survey of Khamisiyah veterans. He discussed the groups they would be using in that survey.

Dr. Sullivan recommended that he consider doing a survey of the group that was most exposed to sarin. She noted the importance in understanding the effects of sarin exposure now that we know that veterans have been exposed to sarin in the more recent deployments to Iraq. Dr. Bossarte thanked her for this recommendation. Mr. Bunker asked if they had been monitoring those who have brain tumors and brain cancer. Dr. Bossarte said that they had, but again addressed the limitation that unless the veteran was seen at the VA, that they did not have that information. He said that the VA OPH was trying to understand that association but that their ability to was limited by this constraint.

Dr. Bossarte concluded his presentation.

**Current OPH Efforts to Better Understand Gulf War Illness**
**Dr. Erin Dursa**

Dr. Erin Dursa spoke following Dr. Bossarte. Her presentation slides can be found in **Appendix B – Presentation 3.**

She provided a brief background on Gulf War illness. She commented on how at that point in time, there was still no single agreed upon and validated case definition, but that in 2013 the IOM recommended the VA use the two most widely used case definitions, which are the CDC and Kansas definitions.

It was recommended that the VA examine existing administrative and clinical data to identify elements that are missing from the CDC and Kansas case definitions and should consider other symptoms and measures that may not be captured by the existing criteria. Dr. Dursa then described the elements of the two definitions: the CDC Definition (Fukuda) and the Kansas Definition (Steele).

She described the challenges of defining Gulf War Illness in 2015, including that the cohort of veterans who served in 1991 are aging and are at risk for development of age-related health conditions. She noted that the onset of age-related disorders may impact the identification of GWI, as age may cause or exacerbate symptoms consistent with GWI such as cognitive function, pain, and fatigue. Thus, she stated that careful consideration must be given to the onset of chronic health conditions that may be simultaneously characteristic of GWI, are routinely reported at higher prevalence among those with history of military service, and are normally

associated with diseases of aging. Also, Dr. Dursa said that caution should be taken to avoid excluding veterans from the GWI case definition because they have a chronic illness, as it is possible that GWI can be co-morbid with other conditions.

She considered whether, moving forward, there should be an endpoint in the Kansas criteria. For example, should symptoms that developed in 2005 or 2010 be considered symptoms associated with GWI? This poses a challenge. Other challenges she mentioned include defining symptom severity or other symptoms that are not captured by the CDC and Kansas definitions.

She then introduced the GWI Discriminate Analysis Project, the goals of which are to (1) integrate multiple VA datasets to develop a data rich cohort; (2) use a multi-symptom process to identify those with probable GWI; (3) determine any additional features of GWI not currently in the CDC and Kansas definitions; (4) test and validate the model; and (5) evaluate in the clinical population. She stated that this was a collaborative effort with Office of Analytics and Business Intelligence and discussed the staffing of the project. She then delivered an overview of the methods and data sets that they would be using in this project. She began by identifying the five data sources used for the study. She then went into detail by discussing each of the studies used as data sources and specifically what data each source provided for the GWI Discriminate Analysis Project. She addressed the advantage of integrating these multiple data sets, which was that it filled the gaps and dramatically increased the sample size.

In the methods, she said that they'd identified three different cohorts of veterans with and without indicators of GWI and described those cohorts. She continued by outlining the list of methods, which can be seen in Appendix B – Presentation 3, pages 10-12.

She next discussed the preliminary results, the findings from the first run on the OPH Gulf War and Gulf War Era Rosters. Multiple factors were found that distinguished Gulf War Veterans (deployed) from Gulf War-Era Veterans (non-deployed). These factors were classified by a physician into the following six domains: rheumatic, gastrointestinal, dermatologic, chronic fatigue symptoms, mental health, and neurologic.

She concluded by discussing the next steps. She stated that the VA OPH would continue analysis to refine the model, integrating data from the OPH GW surveys, the GW registry, and the electronic medical record. She asked the RAC for suggestions on exclusionary medical conditions. Dr. Klimas responded, citing a paper (*Reeves, 2000*) that gave a good review of exclusionary criteria. However, she stated that her reaction to this case was to be more inclusive and to deal with comorbidities as subgroup categories. She suggested dealing with comorbid conditions by powering up the studies enough.

Dr. Dursa continued, stating that other 'next steps' included changing the language used to analyze information in the "clinical notes" section of the VA electronic medical record and considering the option of getting information in the future from those using Medicare and Medicaid to try to obtain information from non-VA users.

She concluded, gave her contact information, and welcomed any suggestions or comments from the Committee.

Dr. Sullivan addressed the issue of exclusionary criteria and commented that Dr. Steele had relaxed some of the exclusion criteria (such as a chronic illness) because at this age, veterans were beginning to develop conditions that the general population exhibits as well. Dr. Dursa said she would follow up on that and discuss it with her. Dr. Sullivan reiterated how pleased she was that the VA was doing these analyses and how crucial they would be, specifically because the Committee had previously recommended that the VA conduct a longitudinal study as well as look across the large data sets that they have access to.

Dr. Hauser asked whether they had a cabinet or group of advisors that they met with regularly and may rely on. Dr. Dursa responded that at that point in time they did not, but that it would be important to have such a panel going forward.

Dr. Klimas had a few comments. First, she lauded Dr. Dursa for this study. She said that she was very excited about it. Second, she suggested that a working group with representatives from Dr. Dursa's group and members of the DOD be established to come up with a case definition. Third, she mentioned some people who were also working on complex case definitions that Dr. Dursa may want to consult if she needed expertise including Dr. Beth Unger at the CDC.

Dr. Erikson next commented that this study showed that the VA was making the aggressive effort that the Committee had wanted to see the VA make. He thanked the RAC and said that he appreciated their council and advice. He mentioned that the Secretary commissioned a technical workgroup to look specifically at GW veterans' experience with relation to brain cancer. The data was preliminary and thus would not be presented, but he said that the Committee could expect it to be analyzed before the next RAC meeting.

Dr. Hauser asked Dr. Erikson about the adequacy of the internal resources and whether they allowed the VA OPH to maximize the trajectory, as far as this project went. He answered that his resources accentuated that this study was a priority.

The Committee took a short break before reconvening.

**VA GWI Research Program Discussion**
**Dr. Stephen Hauser, Chairman**

Before going around and having each Committee member state a single, actionable recommendation, Dr. Klimas suggested that the Committee create a schema of all the recommendations made historically by this Committee and all the outcomes of them. This would indicate for how many years the Committee was recommending the same thing and would create a record of when such recommendations were implemented. Dr. Sullivan and Dr. Hauser agreed that this would be useful and help the Committee and so would create one.

Now, the Committee members each took their turn supplying a single, actionable recommendation. Dr. Klimas went first and asked that the research service form a working group to assist in the development of a single case definition and to review the assessment variables and outcome variables. She gave another recommendation, which was hoping that the research

and clinical sides would collaborate.

Dr. Sullivan's recommendation was for all future genetic studies to look not just at genetics, but also at gene-exposure outcomes, as Dr. Steele's presentation elegantly highlighted the importance of this. She also noted that the population of GW veterans with the greatest sarin exposure is at the highest risk of brain cancer, and so she recommended that this group be followed as a surveillance group. Lastly, she noted that the way the deployed and non-deployed groups had historically been categorized was problematic and needed to be corrected. She noted that this was recommended at the last meeting, and was an important item that needed to be recommended again.

Mr. Bunker first noted that researchers should identify that the Gulf War Desert Storm actually ended April 11th and not March 1st and that this needed to be recognized. Second, he suggested that the VA look at the Gulf War-deployed marines very closely and see what kinds of health issues the Marine Corps still have. In general, his recommendation was that in addition to self-reported outcomes, researchers obtain up-to-date results of physical evaluations.

Dr. Crawford said that a meeting with people from the clinical side would be very important. In addition, she suggested that a mechanism is needed for our veterans to easily be able to contribute to studies such as biomarker studies. She discussed how she had been in the middle of setting up a single process at the Tampa VA for obtaining consent, blood collection, and processing. She said that such a mechanism should be put in place at other VAs. Thirdly, she recommended that at future meetings the Committee schedule more time for public comment.

Ms. Perez-Wilhite liked Dr. Klimas' earlier suggestion and so also recommended that all VA physicians be required to have GWI training to create some uniformity throughout the agency and uniformity of treatment.

Dr. Golomb suggested an analysis be done by the VA looking at mortality of Parkinson's disease and multiple sclerosis in GW veterans broken down by specific exposure subgroups.

Dr. Hauser's recommendations were to (1) consider performing an independent confirmation of the reported association of rare BChE variants associated with GWI in deployed veterans stratified based on their self-reported exposure histories; (2) consider the feasibility of sequencing the entire gene (both exons and introns) and extend this to other candidate genes (such as PON1, PON2, and PON3); (3) consider other repositories that can be used for this (including MVP, for example, or coupled with the DOD serum repository); and finally, (4) consider extending this to ALS where rare PON variants are also associated with disease.

Nancy Klimas commented on this, saying that it falls on the VA and not the DOD to do validation studies and that the Committee needed to consider this policy.

**Public Comment**

Mark Panzetta spoke first at public comment. He is a GW veteran. He described his frustration after going many places seeking treatment and help and not receiving anything.

Ronald Brown, President of the National Gulf War Resource Center, spoke next for public comment. He declared that he understood the importance of research, supported it, and knew it was the only way we will find a cure or a treatment for a better quality of life. Yet, he questioned what we have gained from the research. He stated that $520 million have been spent on GWI research by various agencies. He expressed that there had been many promising pilot studies which had merited follow-up studies to validate the findings. His problem, though, was that many of these promising pilot studies had been "sitting on shelves collecting dust." He said that something must change. He said that promising pilot studies that were not followed up was unacceptable and that these research-based treatments must be validated, because the GW veteran population needed research-based treatment as soon as possible. He asked that the Committee and VA prioritize studies that merit replication on a larger scale and that the VA follow the advice of the RAC and follow up on such studies that merit replication.

Valerie Mullikan spoke next for public comment. She spoke regarding points she did not hear discussed over the past two days that she felt to be very vital. She is the wife of a disabled GW veteran and discussed the disruption of life of veterans suffering from GWI. She mentioned the amount that veterans with GWI sweat. She said this symptom in particular had been very disrupting. She also mentioned that her life had been disrupted because she now had conditions such as fibromyalgia that she did not have before. She said she was also experiencing burning semen syndrome, yet stated that no gynecologist in her area of southwest Ohio knew anything about this syndrome. She said that she knew she was not the only one suffering from this, yet felt that it was not being acknowledged or researched. These two things in combination led her to believe that there is an infectious disease component of GWI. She stated that the exchange of bodily fluids and how GWI affects the spouses of veterans and their children needed to be examined. Lastly, she voiced her frustration that treatment for one facet of the illness with drugs in turn creates a variety of other symptoms due to the drug's side effects. She concluded by petitioning that the RAC investigate whether there is an infectious disease component to GWI.

Anthony Hardie spoke next for public comment. He thanked the chairman, Committee, and welcomed the new Committee members. He encouraged that they not forget that this Committee stemmed from the VA and DOD, who historically denied GW veterans' experiences, exposures, and testimonies. Thus, he advised that the Committee never let the VA or DOD encroach on them, as this Committee was created as part of a checks and balances. He stated that it'd been years and that although repeated recommendations had been made, there was still no coherent federal research strategy regarding GWI (or that if there was one, it had yet to be implemented). He stated that we needed to get to the point where we could have accurate testing for chemical agents that were in the Iraqi arsenal in 1990, both for National Security reasons and for veterans' health reasons. He urged that researchers find biomarkers for exposure and biomarkers for illness, and called on the Committee to call on the VA Secretary to lead a national effort to develop those biomarkers and develop effective treatments for those chemicals known to be in the Iraqi warfare arsenal. He also urged that the Committee tell the VA to follow the IOM recommendation and refer to the syndrome "Gulf War Illness." He also recommended that an investigation is conducted into those who lost the data from the registry and that those found responsible are held accountable. He thanked the Committee and stated that he intended on submitting a written statement.

Marsha Young spoke next for public comment. She stated that she was there to represent American allies, because our allies' veterans with GWI are sick as well yet no one was speaking up for them. She questioned whether the Committee had collaborated with the allies at the administration level or the research level. She stated that she had been collaborating with the allies and had contacted a naval person in the Australian GW Veteran Association. In honor of him, she donated a submission concerning GWI to the RAC Committee. She said that in 2009, a United States and Australian joint research effort was approved yet the aspects of the research were women, younger veterans, and mental health. She noted that there had not been any collaborative efforts on GWI. She asked the Committee to follow-up and to collaborate with our allies on all levels.

Denise Nichols spoke next for public comment. She thanked the Committee and said that she appreciated their work. She re-emphasized that she wanted to have the clinicians and researchers collaborate more to translate research into clinical care. She also suggested training young doctors and nurses on treating GWI and getting more experts involved in GWI may help in clinical implementation. She also suggested placing an emphasis on the children that are now ill. She said that veterans were beginning to give up hope, and that there was a sense of moral injury among them. She said that we were losing time and losing lives, so every resource should be used to try to give veterans help in the clinical area and get them access to testing. She concluded by mentioning some of the past successes that the military had made in the clinical arena, so she was confident that we could tackle GWI and that the successes would stretch into the future and also affect Vietnam veterans exposed to agent orange as well as civilians with environmental exposures. She submitted a public comment in writing: **Appendix C – Document 2.**

Douglas Bartholemew spoke next for public comment. He thanked the Committee and said that while his first and second wife didn't get GWI, his first child was born deformed. He stated that he believed that GWI is transmittable by semen and that his current girlfriend had symptoms of chronic fatigue syndrome. He appreciated the work done by the Committee, but said that the research was not being accounted for because he would still go into to the VA and be treated like a "liar." He said that their research needed to be disseminated to every VA hospital and outpatient clinic and that the VA doctors needed to be educated on GWI. He concluded, expressing his frustration of never receiving a diagnosis after visiting multiple doctors.

Terry McCullough spoke next for public comment. He mentioned that at the last RAC meeting, the veterans were instructed to educate their providers and primary care physicians and that he had tried to relay to them the information he'd found. He requested that the Committee further educate the doctors. He recommended that the Committee ensure primary care physicians know the current research, even if it was just hanging posters in hospitals, to let the doctors know that veterans with GWI exist.

Jay Thomas spoke next for public comment. He asked whether it would be listed in a veteran's records or in their prescriptions if that person was in a DSIG. He was told to email rac@bu.edu and that the Committee staff would follow up on that question. He said that it'd be helpful to have more WRIISC centers or WRIISC hospitals so that those who were far away from the nearest center could still get the help they needed.

Ed Bryan spoke next for public comment. He stated that referrals to WRIISC were not being done and should be done at all clinics. He also said that GW veterans should be seen by doctors first for environmental and neurology consults, and then consulted to primary care, so that the environmental and neurology doctors could provide better direction to the primary care doctors. He emailed the RAC email account with further comments for the record: **Appendix C – Document 3.**

Shawn Scott submitted a written statement to be included in the record (**Appendix C – Document 4a**). His statement is supported by a testimony written by Marilyn McAllister, Lieutenant Colonel United States Army Retired US Paratrooper (**Appendix C – Document 4b)**.

Chairman Hauser regretted to say that the Committee must close public comment for the sake of time. He apologized to those who did not get a chance to speak. He stated that the Committee was resolved to have more time dedicated to public comment at the next RAC meeting. Dr. Hauser thanked the Committee members and everyone who stayed for the meeting. With that, the meeting was adjourned.