

**Minutes of the Research Advisory Committee
on Gulf War Veterans' Illnesses Meeting**

January 31-February 1, 2012

Washington, DC

RAC-GWVI

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Attendance Record

Members of the Committee

James Binns, Chairman
Roberta White, Scientific Director
Carolee Barlow
Beatrice Golomb
Anthony Hardie
Marguerite Knox
William Meggs
Jack Melling
James O'Callaghan
Lea Steele

Members of National Research Advisory Council

Ann C. Bonham
John P. Donoghue
David Korn
Christine Laine

Gulf War Steering Committee

Maximillian Buja, Chairman
Tilo Grosser
Loren Koller

Committee Staff

Kimberly Sullivan
Arpita Husain

Designated Federal Officer

Victor Kalasinsky
William Goldberg

Guest Speakers

James Baraniuk

Mian Li

Julia Golier

VA Office of Research and Development

Robert Jaeger

Victor Kalasinsky

Joel Kupersmith

Abbreviations

ACTH - Adrenocorticotropic Hormone

ALS - Amyotrophic Lateral Sclerosis

CBT – Cognitive Behavioral Therapy

CRF - Corticotrophin-Releasing Factor

CDMRP - Congressionally Directed Medical Research Program

CFS – Chronic Fatigue Syndrome

CPAP - Continuous Positive Airway Pressure

DoD – Department of Defense

DST - Dexamethasone Suppression Test

GW – Gulf War

GWII – Gulf War Illness

HHS – Health and Human Services

HPA – Hypothalamic-Pituitary-Adrenal

IBS – Irritable Bowel Syndrome

IOM – Institute of Medicine

MAVERIC – Massachusetts Veterans Epidemiology Research and Information Center

MRI – Magnetic Resonance Imaging

NRAC – National Research Advisory Council

OEF/OIF – Operation Enduring Freedom/Operation Iraqi Freedom

ORD – Veterans Affairs Office of Research and Development

PB – Pyridostigmine Bromide

PTSD – Post-Traumatic Stress Disorder

RAC – Research Advisory Committee on Gulf War Veterans' Illnesses

RFA – Request for Application

VA - Veterans Affairs

VHA – Veterans Health Administration

WRIISC – War-Related Illness and Injury Study Center

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

January 31, 2012

Lafayette Building, 811 Vermont Ave., NW, Room 1143, Washington, DC

Agenda

Tuesday, January 31, 2012

The first day is a joint meeting with the VA Gulf War Steering Committee and the VA National Research Advisory Committee.

8:00 – 8:30 Informal gathering, coffee

8:30 – 8:40 Welcome, introductory remarks

Mr. James Binns, Chairman

Rsch Adv Cmte GWV Illnesses

Dr. Maximillian Buja, Chairman

Gulf War Rsch Steering Committee

Dr. Richard Wenzel, Chairman

National Research Adv Cmte

**8:40 – 10:30 Discussion: VA Gulf War
Research Strategic Plan**

Dr. Maximillian Buja

Gulf War Research Steering Committee

10:30 – 10:45 Break

**10:45 – 12:15 Discussion: VA Gulf War
Research Strategic Plan**

Dr. Maximillian Buja

Gulf War Research Steering Committee

12:15 - 1:15 Lunch

**1:15 – 3:00 Discussion: VA Gulf War
Strategic Plan**

Dr. Maximillian Buja

Gulf War Research Steering Committee

3:00 – 3:15 Break

**3:15 – 3:45 Update of VA Gulf War research
funding**

Dr. Victor Kalasinsky

VA Office of Research and Development

3:45 - 4:15 Public comment

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

February 1, 2012

Lafayette Building, 811 Vermont Ave., NW, Room 1143, Washington, DC

Agenda

Wednesday, February 1, 2012

- 8:00 – 8:15** **Informal gathering, coffee**
- 8:15 – 9:15** **Committee Discussion: 2012 Planning** **Mr. James Binns, Chairman**
Dr. Kimberly Sullivan
Res Adv Cmte GWV Illnesses
- 9:15 – 10:00** **Washington WRIISC research updates** **Dr. Mian Li**
VA Washington, DC
- 10:00 – 10:15** **Break**
- 10:15 – 11:00** **The HPA axis in Gulf War Veterans** **Dr. Julia Golier**
James J. Peters Bronx VAMC
- 11:00 – 11:45** **Cerebrospinal fluid markers in GW illness** **Dr. James Baraniuk**
Georgetown University
- 11:45 – 12:15** **Public comment**
- 12:15** **Adjourn**

DAY 1

The January 31, 2012 meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses (hereinafter referred to as the Committee) was held in Room 1143 at the Lafayette Building, 811 Vermont Avenue, NW, Washington, D.C.

Welcome, Introductions & Opening Remarks

Mr. James Binns, Committee Chair

Chairman James Binns called the meeting to order at 8:30 AM. He welcomed the representatives of the Gulf War Steering Committee, the National Research Advisory Council (NRAC) and the Office of Research and Development (ORD). A moment of silence was held for the recognition of veterans who had not returned, who had passed away in the last twenty-one years, and for those still struggling with illness.

Following the moment of silence, he announced that the purpose of the first day of the meeting was to discuss and review the VA Gulf War draft strategic plan for the next 5 years of Gulf War related research. Chairman Binns stated that the main goal of this plan was to refocus Gulf War research on multi-symptom illness and to find specific treatments for it.

Discussion: VA Gulf War Research Strategic Plan

Dr. Maximilian Buja, Chairman of the Gulf War Steering Committee, commenced the discussion of the draft Gulf War strategic plan (Appendix B, Document 1). He indicated that the original draft was a good start, but that there needed to be more detail in terms of future research plans in the eight major goal areas. He then introduced two new members of the VA Office of Research and Development, Dr. Robert Jaeger and Dr. Victor Kalasinsky.

Dr. Buja mentioned that the working groups of Gulf War researchers and VA staff were created to address the different components of the strategic plan. He added that the coordinating committee, with the representation of the various working groups, would bring together the individual pieces of the strategic plan into a coherent whole.

Dr. Joel Kupersmith, VA Chief Research and Development Officer, thanked everyone for their efforts and hoped that after this meeting the strategic plan would become more defined and cohesive. He indicated that after the review of the plan by the committees and ORD, the strategic plan would have to be operationalized and a budget for every part of the plan would be crafted. The plan would be a five year plan and every year, certain milestones would need to be met. He also indicated that individual staff members would be responsible for their different components of the strategic plan and that their performance plans would reflect that.

In response, Dr. Buja gave his thanks and indicated that there were about 45 recommendations and subcomponents to them in the draft strategic plan for review during this meeting session. He summarized the introduction to the plan. He indicated that the group also needed to discuss the use of the wording "Gulf War Illnesses" versus "Gulf War Illness" because it had been changed

administratively from the original drafts and was not the intention of some of the authors of the strategic plan sections. He stated that the strategic plan text should start with symptomatic and specific treatments for Gulf War Illness, and then the other sections including databases, case definitions, genetics, biomarkers, animal models, coordination and the concept of translating science into practice would follow for Committee discussion.

Dr. David Korn, from the National Research Advisory Council (NRAC), asked if it was feasible to have a brief summary of what had been gained in terms of sixteen years of research and half a billion dollars of support for Gulf War-related illness.

Dr. Roberta White, the Committee's Scientific Director replied. She started working with Gulf War veterans from the Fort Devens cohort shortly after their return from deployment in 1991. Dr. White stated that people were not sure what was the cause of the illness initially, and the possibilities included chemical exposures, post-traumatic stress disorder (PTSD), and infectious diseases. From this cohort, the rate of PTSD was very low in Gulf War veterans returning from the war, and very low in the high-symptom group. She also stated that what happened over time was that the strength of the signal relating chemical exposures to GWI through brain imaging findings, cognitive findings and symptomatic findings became stronger and resembled a chemical induced encephalopathy. She also stated that microglial changes, acetylcholinesterase inhibition, and other mechanisms were now being investigated to help explain the varied symptoms of GWI.

Dr. Lea Steele, a member of the Committee, stated that devising treatments for GWI was a very challenging area. She described two large multicenter trials conducted by VA that studied antibiotic therapy as well as exercise and cognitive behavioral therapy (CBT). There were some positive results with CBT but very minor when compared to similar symptomatic disorders. Dr. Steele also described a recent continuous positive airway pressure (CPAP) pilot study for disordered breathing that was conducted in GW veterans which showed some benefit to the veterans. In 2006, the Congressionally Directed Medical Research Program (CDMRP) program at the DoD also initiated a GWI research program, and since that time has funded nine treatment studies of GWI in addition to several animal treatment studies. A pilot study of the supplement co-enzyme Q10 has recently been completed that showed an improvement in some of the symptoms of GWI.

Mr. Hardie, a member of the Committee, stated that one of the key issues with the veteran community was deep distrust since it seemed that the bulk of past government efforts were aimed more at proving that there was nothing wrong with Gulf War veterans rather than providing answers for their illness. He remarked that although more than 300 million dollars had been spent by the government on scientific research, to the veteran community it did not seem that the government understood that they were ill and suffering. He commented that the strategic plan was a way to move forward, and the plan could be different from past VA programs because it was focused on improving the health and lives of ill Gulf War veterans. He stated that this plan was also different because this plan had resulted from the work of dozens of people, including outside experts from the Committee along with VA staff, who have worked together through a variety of committees and subcommittees to compile the plan. He stated that this inclusive and consensus driven process was the key to success for improving the health of GW veterans.

Dr. Kupersmith agreed that this must be an implementable strategic plan with built-in performance measures to ensure its success.

Dr. Buja then summarized sections two, three and four of the strategic plan. He stated that the amount of money used for GW research stated in section 4.1 of the strategic plan (Appendix B, Document 1) could be debated as to optimal use of the funds, but at least 400 million dollars had gone towards Gulf War research in various categories including the VA, the University of Texas Southwestern (UTSW) contract, the Department of Defense (DoD) and the Department of Health and Human Services (HHS). He also stated that the reporting of the CDMRP monies lagged about a year behind, so the 2010 reported funding totals for GWI research did not include the CDMRP funding yet but that it eventually would.

Chairman Binns then said that up until 2006, DoD bore the major share of funding for GWI research and this was managed through the defense budget. Since then, Congress had voted each year to continue GWI research at DoD and it had been placed under the CDMRP for this reason. Chairman Binns said that last summer, there was a bipartisan vote in the House of Representatives to pass an amendment that increased the budget for the GWI research program at CDMRP from eight to ten million dollars. He commented that this had been an encouraging indication to researchers and veterans that Congress remained invested in the issue of Gulf War veterans' health.

Dr. Korn then stated that it was his pleasure to work on subsections of this report and that he felt that everyone that participated in devising the plan had a firm commitment that the illnesses of the veteran cohort were real and that there needed to be an effort to find out why this happened and to find effective remedies to mitigate or treat it successfully.

Dr. Buja then moved on to the first objective of the strategic plan as stated in section 5.1 Symptomatic and Specific Treatments of the draft plan (Appendix B, Document 1). The first recommendation, as it was originally written, called for the creation of a Gulf War Treatment Research Center, but the coordinating committee changed it by adding the phrase "coordinating center." The coordinating center would focus on identifying hypotheses that could lead to pilot and other treatment studies. He indicated that this section had a yellow highlight in the text, which meant that it was not within ORD's authority to institute this recommendation, but he was unsure why it was not under their authority. He also stated the other recommendations in this section included clearly denoting Gulf War veterans in the VA electronic medical record as an at-risk group that could benefit from enhanced preventative medical care interventions including smoking cessation and other public health programs. He commented that this section also advised using a well-defined case definition in all treatment trials in order to compare treatment results among different studies.

Dr. Carolee Barlow, a member of the Committee, asked how the strategic plan would ensure that the clinical data would be available, given that it may not necessarily be completely under ORD's control. She also stated that a backup strategy should be devised that could be implemented in the event that they could not get buy-in for getting electronic medical records from other VA departments.

Dr. Buja said that the proposition was to add some fields to various components of the electronic medical record that would identify key bits of information such as if the patient was a Gulf War veteran and to flag them for preventative care. Dr. Beatrice Golomb, a member of the Committee, mentioned that the Committee should keep in mind that the definition of Gulf War era was not confined to the first Gulf War however and could confuse Gulf War with Iraq veterans if not done with this in mind. Dr. Kupersmith indicated that they would have to discuss the issue of defining the Gulf War Era when devising plans for flagging 1991 Gulf War veterans in the electronic medical records.

Dr. Sullivan stated that it was important to identify Gulf War veterans in their medical record, because there are several cohorts that have been followed for a very long time that could be tapped into for further research. She indicated that there were cohorts that could be studied right now for treatment trials that were well-known to established Gulf War researchers.

Dr. Barlow said that it would be helpful to increase the enthusiasm for Gulf War research so that they could implement this plan even if the electronic medical records were not available.

Dr. Steele stated that it was her understanding that a low proportion of Gulf War veterans with multisymptom illness problems went to the VA for treatments, therefore getting the medical records may not ultimately be that helpful. She commented that there was a large database from VA that surveyed 30,000 veterans to find out how they were being treated and if those treatments were effective. She stated that this database could be beneficial to understanding what treatments have been helpful to treat Gulf War veterans.

Dr. Ann Bonham, of the NRAC committee, said that she would hope that VA would learn from what was not done during the Gulf War era in the 1990s so that in the future VA could properly collect data that would be useful for future research. She also wanted to make a note of potential gender based differences in the research cohorts because she did not see that noted in the strategic plan draft.

Mr. Hardie replied that gender and race may have been an issue because in the 1991 Gulf War, ninety-three percent of veterans were male and thirty percent were African American. African Americans were highly overrepresented in the Gulf War compared to African Americans in the US population.

Dr. Victor Kalasinsky, member of VA ORD, then commented on why some of the draft text sections of the strategic plan had been highlighted. He indicated the section in question was highlighted because the word “coordinating center” was added to the text and that the treatment working group members would not have seen the new change had it not been highlighted.

Dr. Sullivan stated that treatment was an important topic and that the treatment working group thought that a treatment center was important to get enough pilot studies started to begin to identify viable treatments for Gulf War Illness. She stated that there needed to be a greater push for pilot studies as a way to identify further full clinical treatments in the most expedient way. The idea was to generate about 20 pilot studies in the discussed 5-year strategic planning period.

Dr. Korn asked Dr. Sullivan if there were therapies known for the individual symptoms in the GWI clusters, and if there were, why had they not been given to veterans.

Dr. Sullivan said that some specific treatments, such as for treating joint pain, were helpful while other treatments for specific symptoms have not proven helpful for treating Gulf War veterans. She explained that there are other symptoms clusters that are unique to Gulf War veterans and that the Committee would like to see a mechanistic based treatment focus so that clinicians can treat all of the symptoms of GWI at once, if possible.

Dr. William Meggs, member of the Committee, said that the Gulf War veterans he sees are treated extensively in a symptom based way and were treated with opioids for chronic pain. He also said that they were receiving Selective Serotonin Reuptake Inhibitors (SSRI's) and seizure medications in an effort to control their symptoms, but in the veterans that he had seen, they were still ill and still suffering greatly in spite of the poly pharmaceutical approach. Dr. Meggs stated that he had a long interest in the environmental medicine approach and had seen dramatic successes in people with similar illnesses with the combination of clean air, organic foods, exercise, and sauna therapy.

Dr. Golomb stated that there was no reason to think that other treatments for similar conditions would not be equally effective among those with GWI but that she thought that it had not been assessed in a systematic way. She also remarked that another complicating issue was the possible varying etiologies for GWI.

Dr. Barlow said that one of the weaknesses that she had seen was the failure to truly run clinical trials with drugs that were already available to see if they address one or more of the symptoms of ill Gulf War veterans. She stated that a critical thing to help veterans now was well controlled studies using existing therapies in order to identify if they were beneficial. Dr. Steele agreed with Dr. Barlow, but replied that the problem was that there were currently no data on what might be useful in terms of symptom-based therapy, and that this data needed to be collected.

Dr. Meggs said that one problem of implementing such a strategy was that Gulf War veterans often take many drugs and it is very difficult to find a "pure" GWI veteran, especially since many have developed co-morbidities that increase in an aging population.

Dr. Buja transitioned the discussion to the second goal of section 5.1.5 of the strategic plan which called for a research center with a budget that could fund twenty pilot treatment trials. He stated that the coordinating committee felt that this plan was too ambitious, and that the plan was modified to have a coordinating center to see what was available for possible treatments, and to then coordinate the dissemination of these treatment trials in some coherent strategy.

Dr. Sullivan asked if that meant that individual investigators would continue to put in for individual treatment trials, and then the results would be coordinated. Dr. Buja replied it could be similar to the NIH strategy where there are program project grants, which are investigator-initiated, or NIH scores where there is a national effort on a topic directed by the NIH.

Dr. Barlow suggested funding ten pilot treatment trials and ten big trials if twenty trials seemed overwhelming.

Dr. Buja then asked why a treatment trial center was needed. Dr. Sullivan responded that a center was not necessarily needed but a push was needed to get more treatment trials initiated. She stated that VA should consider coordinating this as a top-down approach to encourage more pilot treatment studies. Dr. Barlow responded that with the top-down approach it would be possible to find a good patient population that could be incorporated for extension to larger trials.

Dr. Robert Jaeger, a member of VA ORD, said that it was his understanding that the Institute of Medicine (IOM) was working on a new report entitled “Gulf War and Health - Treatment of Chronic Multisymptom Illness,” where the IOM was reviewing the available treatment literature for CMI and he believed that the review and their recommendations for further treatment considerations was due out in December 2012.

Dr. Buja stated that the group should discuss if the word coordinating center should be added to the draft strategic plan text, and if it should be a VA-directed initiative to identify and fund these twenty pilot studies. He added that having VA as the site of the coordinating committee was a suggestion, but other locations could be possible.

Dr. Steele said that a developmental step was first needed before moving onto large trials. She also stated that she saw some disconnect in this section because despite the language regarding having a center and having a coordinated effort, in the end, the funding mechanism for symptomatic and specific treatments would initially be funded through RFAs and other federal agencies, followed by cooperative studies (CSP) development of multi-type trials.

Dr. Korn wanted further clarification because he said that several people had stated the symptomatic treatment approaches had been studied. Dr. Steele clarified and said not studied, just tried clinically and good data was not available on them.

Dr. Tilo Grosser, from University of Pennsylvania, asked why these symptomatic types of trials had not developed organically. He also asked what made everyone think that directed trials would result in quality research.

Chairman Binns did not have an answer regarding Dr. Grosser’s research quality question, but he replied that Dr. Kupersmith had emphasized that it was difficult to get investigators interested in Gulf War research because it was stigmatized in earlier years and a directed approach may help with getting researchers interested in the GWI field. Dr. Golomb agreed with Chairman Binns and said there was a VA training document that she believed taught VA physicians that Gulf War veterans were not really ill.

Dr. Sullivan stated that she knew of some individual investigators who had put in for full treatment trials regarding Gulf War research and the reviewers said the study was not ready for a full treatment trial and it should be funded as a pilot study. She added that since VA did not fund pilot treatment trials for GWI, these investigators often did not come back to competing for GWI research funds through the VA.

Mr. Hardie said that he was on the CDMRP panel and that the research proposals at CDMRP are open to non-VA researchers and from what he understood, VA only funded VA researchers. He believed that the VA system may not be equipped to set up these types of treatment trials without outside investigator partnerships. Dr. Steele added that the smaller treatment pilot studies for GWI done by VA investigators are funded by DoD and not by VA.

Dr. James O'Callaghan, member of the Committee, added that many VA researchers do not compete for the internal VA RFA's, but they do compete for CDMRP funds. He stated that VA needed to find a way to make sure that there was enough partnering within and outside the VA clinical research community to get these trials developed and funded.

Dr. Jack Melling, member of the Committee, said that philosophical differences between investigator-initiated research versus directed research was an issue. Dr. Bonham said that given the philosophical differences, she thought it would be very helpful to have an outside body of scientists review the pilot studies, instead of those that are doing the pilot studies or receiving the money. Dr. Sullivan agreed that was a good idea.

Dr. Buja added that the draft strategic plan called for both of these strategies. It called for starting with RFAs and investigator-initiated research, and then moving on to the Cooperative Studies Program (CSP) and the Cooperative Clinical Trial Awards, which would be the central approach.

Dr. Sullivan said that the two were not mutually exclusive and the idea was to have some sort of center or coordination for all of the treatment trials.

Dr. Barlow added that there needed to be external and investigator review of data to insure quality. Dr. Bonham agreed, but clarified that she also meant an outside panel should be used to look across the studies and to look for real outcomes.

Dr. Buja had comments regarding priorities for the further recommendations in section 5.1.5 including smoking cessation, complementary and alternative medicine, and cognitive rehabilitation therapy. He stated that if the coordinating committee had the Gulf War research money and was going to distribute it, they would not distribute very much to those elements since it would likely not be possible to fund everything that was recommended. Dr. Sullivan said that it was clear that Gulf War veterans are ill and they are an at-risk group already for other co-morbid illnesses so the treatment working group felt that it was important to think of preventative medical care as well as therapies for their current symptoms. She replied that although smoking cessation seemed like a small matter, it could make a large difference in the health of these veterans as they continue to age. She added that these were simple things to address and fix future potential health problems.

Dr. Buja asked whether these elements should be funded from a limited amount of Gulf War specific money. He also added that in his view, that somebody else needed to fund these elements because they were not directly linked to GWI. Dr. Sullivan replied that flagging these veterans for further health prevention strategies in the electronic medical record and letting preventative health funds pay for this could be a strategy.

Dr. Kalasinsky stated that there were RFA's that are specifically for pilot projects. He continued that in order to help facilitate that, ORD had instituted a Cooperative Studies Program (CSP) that was going to be collecting demographic and health information and blood samples on Gulf War veterans as a mechanism for putting together cohort groups that could be studied by other researchers.

Chairman Binns stated that he did not believe that there was disagreement that both top-down and bottom-up approaches were valid and that funds should be focused more on treatments for Gulf War research.

Dr. Buja then announced a fifteen minute break.

Chairman Binns resumed the meeting and stated that Dr. Jaeger's office was making copies of the draft strategic plan for members of the public to follow, and it was posted on Mr. Hardie's website as well.

Dr. Buja then resumed the meeting by introducing the discussion of the next section of the strategic plan which was the databases and continued surveillance section 5.2 (Appendix B, Document 1). The goals of this section were to enhance ongoing surveillance efforts of Gulf War and Gulf War era veterans, to improve the usefulness of existing databases and to develop new databases to address specific research questions. The first goal of section 5.2.6 of the strategic plan was to expand the surveillance capacity of the VA Office of Public Health (OPH) planned longitudinal survey of 30,000 Gulf War era veterans to collect detailed and systematic data on symptoms associated with Gulf War service, on veteran reported diagnosed diseases, on medical and self-care treatments used by ill veterans, and on VA and non-VA hospitalization and healthcare utilization by this population. Dr. Buja stated that the second goal of the database group was to enhance the statistical reporting capabilities in VA's Gulf War Era pre 9/11 report by adding comparable cohorts including Gulf War veterans who were deployed between 1990 to July 1991. He stated that the third goal was to develop a pharmacovigilance-style surveillance system in the VA electronic medical record to identify emerging trends in health conditions related to Gulf War service. He said the last goal was to develop a treatment identification surveillance system from the VA electronic medical record to identify treatments given to Gulf War veterans that may be suitable for further research.

Dr. Steele endorsed the recommendations of this section and stated that she noted a lot of yellow highlighting in this section of the strategic plan which signified that ORD would need to negotiate with other VA departments to obtain approval for these recommendations. She said that she and the other members of the databases working group had agreed to be part of the strategic planning process and were advising on the strategic plan for overall "VA" Gulf War research, not ORD Gulf War research. She expressed her frustration that the Committee was now hearing that ORD had not coordinated ahead of time for any of these plans and that many more people would need to be consulted before anything could be agreed to.

Dr. Aaron Schneiderman, from the Office of Public Health (OPH), indicated that OPH was involved in the development of the draft strategic plan. Dr. Steele asked if OPH would be following the advice listed under surveillance in the draft plan. Dr. Schneiderman said that

within the context of the activities of the OPH, the elements laid out in the plan would be considered in terms of what were appropriate directions for OPH to take. He could not say that OPH would do everything though.

Dr. Steele asked if data collection efforts by the OPH would be guided by this plan, or if it would have a whole other process. Dr. Schneiderman said that OPH also had a strategic plan process but they would take into consideration this plan.

Chairman Binns said that the OPH Gulf War national survey had produced some of the most important insights in Gulf War research, and that OPH had been good to present to the Committee. However, he added that the Committee currently had no idea if OPH had made any of the recommended changes that the Committee had recommended to OPH at prior meetings.

Dr. Schneiderman replied that OPH did consider the comments provided by the Committee and OPH responded to each of the critiques and changed parts of the survey that raised the concerns of the Committee members. OPH was still awaiting OMB approval for the national survey of GW veterans which was a requirement of the government.

Dr. Sullivan asked if the survey was finalized, and Dr. Schneiderman responded that they were working on the final draft. Chairman Binns asked if the current survey could be shared so that they could see the degree of change that had been made. Dr. Schneiderman said that OPH addressed many of the comments by the Committee, and everything that they said that they would do had been incorporated into the survey.

Dr. Golomb asked if he could provide a copy of the survey to the Committee, to which Dr. Schneiderman said it was not final. Chairman Binns stated that they would like to see it before it was final so that they could make further comments, in which Dr. Schneiderman responded that he would take the request to his department for approval. Dr. Buja asked Dr. Schneiderman whom OPH reported to. Dr. Schneiderman responded that ORD and OPH had the same reporting chain within the Veterans Health Administration (VHA). Dr. Kalasinsky said that his office would work with OPH.

Dr. Golomb asked whom Dr. Schneiderman directly reported to. Dr. Schneiderman said that he reported to the Assistant Deputy Secretary for Health Policy. Dr. Golomb then asked if this was the person the Committee should send requests to. Dr. Schneiderman responded that the thing to appreciate is that the different programmatic offices are responsible for developing strategic plans, which interrelate with the broader administration level plans.

Dr. Sullivan pointed out to Dr. Schneiderman that there were people from his office involved in several of the working committees for the strategic plan, so that although the strategic plan was not final OPH was consulted in the strategic plan development. Dr. Schneiderman agreed that this was accurate.

Dr. Buja moved to the second goal of the database and surveillance working group which was to improve the usefulness of existing databases by linking them and integrating them. The first subgoal called for convening an expert panel to guide in the coordination of data and linkage

efforts at VA. He also stated that since this section was also highlighted in yellow, that he was unclear who had the authority to convene such an expert panel.

Dr. Tim O’Leary, Deputy Chief Research and Development Officer, said that with databases, it depended upon exactly what was required to get to the end goal. Dr. Kupersmith also mentioned that this would involve working with the office of information technology which reported to the assistant secretary and not to ORD. He explained that the assistant secretary had a prioritization process that takes input throughout the different VA departments that require product development. He stated the he was optimistic that the budget would be supportive to meet the increased database and information technology commitments but until the budget was published, that he could not commit that these recommendations would be done. He also stated that regarding the sections in the text that were highlighted in yellow, that it was not that ORD was not committed to them, but that ORD did not have control over these areas. Dr. O’Leary said that Mr. Gingrich, the VA Chief of Staff, was committed to this group and he would certainly try to do what he could to insure that these proposed database and surveillance recommendation could be implemented, but he did not want to make a commitment on behalf of Mr. Gingrich.

Chairman Binns requested that when ORD prepares the annual report to Congress for Gulf War research, that it should focus on Gulf War multisymptom illness and not include some of the additional areas such the ALS and MS research portfolios that had been included in the past so that Congress could get an accurate picture of what fiscal limitations ORD has had to face.

Dr. Grosser asked Dr. O’Leary how he would deal with the highlighted yellow sections of the report going forward.

Dr. O’Leary said that the overall process and the strategic plan itself didn’t constitute advice to his department until it was approved by all of the groups convened for this meeting including the RAC, NRAC and the GWISC.

LTC Marguerite Knox, member of the Committee, said that every day she deals with soldiers as a nurse practitioner and that sharing of data between active duty soldiers, VA, and the Guard simply did not exist.

Dr. Jaeger thanked LTC Knox and agreed with the importance of DoD having a data transfer agreement with VA. Dr. Korn stated that he was on an IOM committee in 1997 and during one meeting, there was almost no way of going to the DoD medical record and VA record. He said that it was disheartening to hear the discussion because instituting a seamless pathway to stream research data back and forth from DoD and VA was the strongest recommendation by that committee from many years ago and it was never done.

Dr. Steele said that it was very hard to integrate these databases, and that it was probably not on the top of the list of the important things. She said one of the important things was that it wasn’t known if Gulf War veterans have higher rates of many diseases, and it was her understanding that VA did not have that data nor had it been collected.

Dr. O'Leary said that he would bring this up to Mr. Gingrich's taskforce, which was committed to making things go forward. Dr. Buja stated that he understood that there may be some limitations on implementing all of the recommendations, but there was nothing in the plan that indicated that ORD must do specific tasks. He added that the strategic plan was simply a logical plan by scientists on how things should be pursued going forward. Dr. Barlow asked if there was a way to make that statement clearer in the strategic plan. Dr. Buja said that it could be suggested.

Chairman Binns said that there was an advantage to the way the plan had proceeded so far as an ORD document. He added that it would be nice if it were an all VA document but that at least ORD was in support of it even if they couldn't speak for the other departments included in the plan.

Dr. Jaeger noted that the genomics, the animal models, and the biomarkers sections were not highlighted in yellow, because he thought that ORD could move forward without getting any other departments approvals for those sections.

Dr. Sullivan said that she understood that combining datasets from different government agencies was a difficult task to do but indicated that perhaps putting a flag in the VA medical record that says this is a Gulf War veteran could be simple enough to do. Dr. Golomb remarked that it was important to flag them as Gulf War veterans if they were in the 1990-1991 conflict. Dr. Sullivan agreed with this suggestion. Dr. Schneiderman added that to make changes in the health record did require a lot of effort and coordination but it was a great idea.

Dr. Kupersmith said that he thought this should be possible to do.

Mr. Hardie asked how to determine that ORD and OPH would be committed to the Gulf War research strategic plan. Dr. Kupersmith stated that it was ORD's plan to discuss it with OPH. Dr. Jaeger asked if NRAC had advisory ability over OPH as well. Dr. Kupersmith said that NRAC advised the Secretary on research issues but he did not know if that was confined to ORD.

Dr. Buja reminded everyone that the intent of the plan was to come with a logical plan that would be as comprehensive as possible and by necessity require multiple arms of the VA to come together to the best extent possible.

Dr. Kupersmith added that this was the strategic plan, not the operational plan. He stated that the working groups could make suggestions regarding operations, but they were just suggestions. He added that he could not make any guarantee that this was going to work, and he could not tell what people from the other departments would say to him when ORD discussed the strategic plan with them, but the preliminary discussions had been very encouraging.

Dr. Barlow indicated that she thought the biggest concern had to do with the lack of information in the longitudinal surveys and asked if they could do something to define clearly what they were looking for in the surveys. Chairman Binns added that the Committee had made recommendations specific to the longitudinal surveys starting in November of 2010, so a lot of emphasis had been given to defining what they are looking for from the longitudinal survey.

Dr. Schneiderman responded that the survey of this year would be the third time they were completing survey data from 30,000 veterans. He stated that they had responded to RAC's critique and made alterations to the current survey.

Dr. Christine Laine, member of NRAC, commented that this plan consisted of a lot of playing catch-up because of poor integration of data sets and poor collection of data in a prospective fashion in the past, and she wondered if this would ultimately be more effective in getting the changes made by the cooperation between different bureaucratic divisions and ultimately help more people in the long term. She added that if the data collection was set up prospectively, they could figure out not only what went wrong here, but also to be more proactive and efficient going forward.

Dr. Kupersmith agreed with Dr. Laine's discussion except for the term bureaucratically since it did not create optimism. He added that ORD was working on all of these things, and how VA research arms could cooperate together.

Dr. Schneiderman said that in response to Dr. Laine, OPH had historically conducted population level surveillance using population based sampling. He said that OPH initiated a similar study in Operation Enduring Freedom and Iraqi Freedom veterans. They were planning to follow this cohort prospectively and planning new studies or a new approach to represent the population experience.

Dr. Buja stated that the most important thing was to get the longitudinal study optimal before launching new databases even though there may be some merit to them. Then he moved onto the case definition section (5.3.1) of the strategic plan (Appendix B, Document 1) for discussion and said that there was a general consensus that this was a well written section and also a very important section of the strategic plan. He then went through the major objectives of this section. The first was that the case definition would be developed by a consensus panel of experts in the field, by utilizing analytical results and comprehensive evaluation of data sources. He stated that the second goal was that the evidence based process would prioritize characteristics specific to specificity, sensitivity and standardization of symptoms assessment in order to identify more homogenous groups and subgroups of symptomatic veterans for research studies. He commented that the third goal was the recommended use of an interim case definition based on the publication regarding the Kansas Gulf War Illness criteria. The fourth goal was that the expert consensus panel would review existing resources for evaluating Gulf War multisymptom illness case definitions and establish criteria for the case definition. The fifth goal, regarding data assessment, was that this should involve a comprehensive analysis to evaluate existing case definitions in relation to priorities identified by the expert panel.

Dr. Steele stated the issue of multiple case definitions for studies was a core methodological issue and problem when comparing results of Gulf War studies. She indicated that defining the case definition of Gulf War Illness was a high priority. Dr. Korn agreed with Dr. Steele and said that researchers needed to identify a rigorous definition for Gulf War Illness to use for biological studies that would follow because if it was not used then researchers would not find the consistent biological targets that they were looking for.

Dr. Golomb offered a different perspective in which she believed that it was critical that data be collected relative to an agreed upon case definition like the Kansas criteria but she also thought it was important that some of the studies included patients who were beyond that scope. She indicated that she would be comfortable with the idea that 2/3 or 3/4 need to meet the Kansas criteria, but it would be prudent to allow some discretion for investigators to go beyond the criteria.

Dr. Korn did not agree with this suggestion because he said that researchers could only begin to identify markers of illness if a strict case criterion were used. He then added that researchers could then expand their inquiries to see if those markers were also informative in a wider population of people who may be more loosely connected with the strict case criteria.

Dr. Barlow said that in regards to developing biomarkers, she strongly agreed with Dr. Korn. She stated that researchers would need to find patients within a very narrow population, or else their clinical trial would fail. Dr. Korn added that he would consider this as a starting point and not an end point. Dr. Golomb agreed with a narrower definition for treatment trials, but thought that with regard to biomarkers, it was a bad idea to include a minimum representation of symptoms.

Mr. Hardie said that the conundrum essentially was that veterans have this chronic multisymptom illness, but the individual symptoms are not unique in veterans suffering from GWI. He said that Gulf War veterans have many individual symptoms but all at the same time which does make it a unique illness. He used the example of HIV with the fact that when HIV was first new, people thought it was cancer, but then people realized it was caused by a virus. He wondered how science looked at making case definitions from this new disease.

Dr. Korn explained that HIV became a pretty typical phenotype and that it took a few years to recognize a number of the manifestations and that HIV wasn't as heterogeneous as GWI phenotypes tend to be.

Mr. Hardie mentioned that a major discussion now is if you were non-deployed, can one have Gulf war illness. He had read a perfect description of GWI, but the veteran that wrote it was not in the 1990-1991 Gulf War. He also added that Dr. Steele's research showed that you have the greatest risk if you served in Kuwait or Iraq. He stated that narrowly defining it would exclude some people but it seemed like that was what had to be done.

Dr. Buja asked if it could ever be boiled down to a paradigm similar to other chronic diseases where subgrouping was allowed, like with the American Rheumatologic Association. Dr. Steele responded that some of the case definitions did just that in different ways in which you could compare people who served, look at their symptom profiles and conduct analytic steps. She added that one of the reasons a member of this group was pushing for the Kansas group definition was because it allowed for subgrouping. Dr. Barlow asked Dr. Steele if that was the recommended case definition for the strategic plan. Dr. Steele said that her case definition working group had recommended the Kansas state definition be used for all research because it had some of the criteria that they wanted.

Chairman Binns called a lunch break. Before breaking, he asked the Committee to recall the IOM statements from their recent report which said that the committee accepted that multisymptom illness was a diagnostic entity. He also mentioned that there had been a general re-editing of the strategic plan sections that were put together by the working groups to pluralize illness throughout the text. He said that illness vs. illnesses had been an important philosophical issue for 21 years and that the IOM had decided it already.

Dr. Korn said that he was on the IOM on countless committees, and that they weigh evidence and they come sometimes easily, and sometimes not very easily, to decisions but, he did not think that the definition section was making a statement that there was one illness or there may be eight or nine variations of the illness.

Chairman Binns said that he was not disagreeing with Dr. Korn but he was saying that the word should be illness not illnesses based on not just the IOM, but also a report from the RAC committee in 2008 that analyzed all the research that was known up to that time and he felt that Gulf War multisymptom illness should be considered a single condition. Dr. Steele agreed that it should be kept singular because the entire epidemiological pattern showed the same pattern of symptoms in Gulf War Illness. Chairman Binns responded that if you define it as Gulf War Multisymptom Illness, then every place else it can be marked GWMI. Dr. Buja said that in the abbreviations section there is "GWVI" in which Chairman Binns responded that the letters GWMI should be used. Dr. Kalasinsky added that there are other illnesses associated with Gulf War veterans and Dr. Steele responded that they were just talking about this one phenomenon. Chairman Binns mentioned that this research program was to address multisymptom illness and not other related illnesses for the strategic plan.

Mr. Hardie added that this committee had dealt with other illnesses as well. Dr. Steele added that for purposes of this symptomatic illness that was not explained by diagnoses, it was more helpful to not call it the generic illnesses because that implied that everything that had happened after the Gulf War could be under that label.

Dr. Barlow said that when you read the strategic plan, it was unclear if it was defined as illness or illnesses. She brought up the example that in one paragraph it talked about developing biomarkers for Gulf War Veteran illnesses. She asked that in that case, would they develop biomarkers for ALS and Parkinson's disease?

Dr. Kalasinsky responded that it depended on whether some of these problems developed later in life are related to immune changes and things of that sort, but they were talking about the whole Gulf War veteran community, not just the ones with multisymptom illness. Dr. Barlow said that Gulf War veterans may be getting additional illnesses as they age, which may or may not be associated with their age. She emphasized that they need to get to the underlying problems that the veterans are facing.

Dr. Kalasinsky said that he appreciated her point but there was also the point that these things do affect Gulf War veterans and they didn't currently know exactly why, and if the development of onset of other conditions were related to multisymptom illness or not.

Dr. Barlow indicated that that would be a different study. She indicated that by keeping the term illnesses as plural, they were decreasing the opportunity for this work to identify a treatment strategy or diagnostic criteria for helping patients with GWI.

Mr. Hardie asked if the plan was now about the health of Gulf War veterans or was this plan still focused on targeting multi symptom illness. Chairman Binns said that the working groups were writing for chronic multisymptom illness and that nothing addressed ALS, except for surveillance, and that was not the idea of the working groups.

Dr. Laine proposed calling it a multisymptom syndrome in which Dr. Steele responded that the discussion of illnesses versus illness was a result of a debate many years ago about whether this should be considered a unique syndrome or not. She added that those who had read the literature would agree that syndrome would be fine, but because of the history and political forces, it became unpopular.

Chairman Binns then announced a lunch break.

After lunch, Dr. Buja then turned the discussion to the next section of the strategic plan, section 5.4, that included genetics, genomics and systems biology (Appendix B, Document 1). He suggested that this section of the plan would be applied to advancing and understanding of the biological networks involved in Gulf War veterans' illness. Dr. Buja then asked Dr. Grosser to comment on the recommendations from the genetics working group.

Dr. Grosser said that his working group had essentially three goals. One goal was to recruit cohorts of veterans prospectively who then could be available for further genetics studies. Investigators would be funded based on investigator initiated mechanisms. The second goal referred to the way studies were to be designed, which was essentially following the most modern guidelines of genetics and genomics studies. The third goal referred to the two cohorts that were currently being assembled by the ORD. He explained that one study was in the pilot study phase which was the Gulf War era cohort and biorepository (CSP 585) study which he envisioned would be the primary source and the earliest available complete source of data to perform genetics studies. He said that he envisioned that the million veteran's program should then be the primary cohort for validation studies.

Dr. Buja expressed his concerns that the larger million veterans study might be conducted in the way that would not yield great values specifically to the Gulf War Veterans' illness investigations. Dr. Grosser replied that was exactly what he had stated under the opportunities and challenges section of the genetics section and had made note of steps to take to make sure the data was actually of value for Gulf War research.

Dr. Steele mentioned that an issue with the million veterans program was that they have already developed standardized instruments and the questionnaires that do not reflect the health symptom data necessary for GWI research.

Dr. Barlow said that it would be great to use the million veterans program to validate any candidates that came out of the Gulf War illness group, but she also recommended that VA validate the results using other high quality Gulf War veteran repositories as well.

Chairman Binns stated that there was a reference to another GW cohort at the very end of section 5.4 of the strategic plan, which he indicated was the brain bank that was originally announced to the committee in 2005. He stated that it had been a very expensive project and that in the last 3 years alone, had used over 7 million dollars of GW funding. However, it proved not to be a GWI brain bank but rather an ALS brain bank. He stated that it was a clear example where ORD needed to shift focus away from spending money on projects that did not relate to chronic multi symptom illness in GW veterans and he suggested that a statement be added that although this was a fine research project, that it should be funded only with funds available outside of the Gulf War research portfolio.

Dr. Barlow agreed with chairman Binns, and Dr. Grosser said he would take out the statement regarding this study. Chairman Binns said that it didn't need to be taken out, but that he would prefer his clarification comment to be added to the text of this section.

Dr. Buja then proceeded to start the discussion of the biomarkers section of the draft strategic plan (Section 5.5). He stated that the language of illness vs. illnesses needed to be reviewed in this section of the strategic plan as well (Appendix B, document 1). The recommendation regarding biomarkers of neurologic and or neurodegenerative effects of GWI and/or neurotoxicant exposures included histopathologic examinations of postmortem human and animal brain tissue, analysis of cerebrospinal fluid, analysis of blood and advanced neuroimaging techniques. This section also proposed a variety of imaging techniques including functional MRI, high resolution structural MRI, diffusion tensor imaging, positron emission tomography and magneto-encephalography. He suggested that this was a large list of recommendations that clearly needed prioritization.

Dr. Sullivan said that it was a long list of recommendations to suggest because the biomarkers working group were trying to build upon places where there were positive results with Gulf War veterans, but she agreed that it needed to be prioritized. She stated that the idea was to build upon the results of prior neurological studies as well as imaging to look at tissue samples with the actual brain bank that would be set up for GW multisymptom illness.

Dr. Buja asked how VA researchers would obtain the post-mortem brains. Dr. Sullivan responded that small numbers of GW veterans were passing every month and if there was a big push to get GW veterans signed up to donate their post-mortem brain and tissue, it would be possible to get some of this tissue in the near future. She indicated that she did not know how many post-mortem brains they would get, or how fast they could be obtained but that even a small amount of brain tissue could give a lot of information about the pathobiology of GWI. Dr. Buja asked where this GWI brain bank was located and Dr. Sullivan responded that it was headed by the MAVERIC group at the Boston VA, but there were several sites around the country that coordinated the individual parts of the brain bank.

Dr. Bonham asked Dr. Sullivan what she wanted the biomarkers to do. Dr. Sullivan responded that they were trying to get some kind of marker to provide a clue to what is going on in the pathology of GWI. Dr. Bonham responded that she had found successful biomarkers in a lot of diseases, but she did not understand how that was going to affect treatment because right now VA is only treating the symptoms of GWI. Dr. Sullivan replied that her working groups were trying to identify diagnostic markers of GWI as well. Dr. O'Callaghan then added that developing biomarkers could feed back on animal research where it would be easier to then screen for treatments. Dr. Sullivan remarked that her working group also thought this was perfect timing to bring animal models into GW research because VA was starting preclinical program projects where they were using animal models to assess these different biomarker facets of GWI research.

Dr. Korn stated that regarding grant applications, it seemed that too much new technology was put together in the strategic plan and indicated that this section needed to be prioritized. He added that it would be great if the prioritization was somewhat informed by matching the marker search with something that was prominent in a significant number of persons with GWI.

Dr. Buja agreed with Dr. Korn. Dr. Buja added that the goal seemed to be to develop biomarkers, but the details were not all there. Dr. Sullivan responded that the group could certainly simplify the text.

Dr. Golomb was concerned about Gulf War money being taken out for equipment. She hoped that if this were implemented, that not all the money would go to the imaging equipment because it would be expensive. She preferred to prioritize the less expensive biomarkers.

Dr. Barlow found that many elements of this section were covered elsewhere in other sections of the strategic plan. She believed that a true pharmacodynamics biomarker initiative was missing in the strategic plan. She believed that there needed to be a focus on finding a biomarker to help define what the disease entity or symptom was that could be targeted and then assessing if modifications to the patient could change that biomarker.

Dr. Buja then asked Dr. Kupersmith and Dr. Kalasinsky if funding biomarker studies would be done through an RFP type mechanism. Dr. Kupersmith said that they didn't have enough money in general to fund this entire strategic plan but he indicated that the plan would need to operate through the RFP mechanism. Chairman Binns suggested that they needed to define how to prioritize these topics.

Dr. Barlow added that VA also needed to get investigators excited about GWI research. Dr. Kupersmith agreed with Dr. Barlow that they need to engage people working in these areas, not just in GWI.

Dr. Grosser said that usually these large biomarker studies were therapeutic studies, and synergy was sought between studies because one of the expensive components of biomarker studies was the study itself. He suggested a mechanism for increasing the synergy between biomarker studies and therapeutic studies or genetic genomic studies so they could be more cost effective.

Dr. Kupersmith responded that it was possible to do that. He also added that there were biomarkers and surrogate endpoints and they needed to distinguish between them. Dr. Grosser indicated that he understood that point, but he wanted to point out that an expensive component of biomarker research was recruiting subjects.

Dr. Jaeger then made a housekeeping comment to say that he had returned with copies of the strategic plan to distribute to the public.

Dr. Steele agreed with Dr. Grosser that recruitment difficulties were a big issue in GWI research and that there was no way to locate them through VA. She suggested that multi-tasking should be done in studies, such as looking at immune function and also looking at brain function in the same study.

Dr. Buja then transitioned the discussion to the animal model section of the strategic plan (section 5.6). This part of the strategic plan included characterization of persistent effects of Gulf War related exposures alone and in combination on sensitive indices of neuropathology using contemporary nerve signals and techniques, neuroinflammatory processes associated with glial activation and CNS autonomic pathology and function, immune parameters, and sensitive indicators of hypothalamic pituitary adrenal axis function.

Dr. O'Callaghan said that these recommendations would be somewhat new for VA researchers. He added that they actually encapsulated in large fashion recommendation from the past RFA from the VA, just updated with the current state of the art for neuroscience. He commented that this was a biomarker program as well, and that they needed to take advantage of the fact that in animal models, you can look at differences over time. He stated that his working group wanted to appeal in an exciting way to the researchers to get them to pursue animal model studies. He also stated that it was a broad enough topic that fit in with a few other ongoing programs, but it was targeted to GWI.

Dr. Buja asked what kind of toxin would be used to create such a model and what would be the preferred species. Dr. O'Callaghan responded that it would stem from what we already know from dosing models that have been used that are outlined in the 2008 report.

Dr. Kupersmith said that he thought it was good to reference what Gulf War veterans were exposed to, but as a plan, he wanted the experts to respond to the RFAs, with their own ideas based on the information that was already known. He was unsure if very specific dosing and methods needed to be in the plan itself.

Dr. Barlow suggested that maybe the text with the ALS example could be exchanged with some language from the 2008 report of other more relevant studies. Dr. O'Callaghan responded that he could exchange the section out.

Dr. Steele had a comment for Dr. Kupersmith regarding the last two sections of the strategic plan. She said that they all agreed to what he said, of not having these sections be too prescriptive and just waiting to see what comes in from the RFA's, but she was not sure how that would differ from what they were currently doing. Dr. Kupersmith responded that it would differ in the sense that they would have a plan to get things done. He added that their obligation was to

get it done as soon as possible and if the RFA doesn't work, they would use other ways. He said that the key thing was to ensure a new cohort of people who had expertise in areas that had not been applied before.

Dr. Steele said that many of these items had been discussed in previous RFA's. Dr. Kupersmith responded that within the RFA and in the investigator-initiated mechanism, his office needed to figure out how they could get this done, either contacting investigators directly, or looking for ways to engage investigators. Dr. O'Callaghan said that there were capable VA researchers that could do this work because they have been funded with CDMRP money in these topic areas and they have the expertise to meet these recommendations and should be approached to apply for VA funds as well.

Dr. Korn suggested that there should be an introduction that says a little bit about what animal studies have contributed to understanding GWI in the last decade and a half then with a transition to the future plan of animal use studies. Dr. Barlow agreed with Dr. Korn's point, and believed that short introductions could be applied to other sections of the draft strategic plan as well. Dr. Kupersmith and Dr. Buja agreed with this plan.

Dr. Korn asked if any of the effects from toxic exposures in creating GWI had been reproduced in animal models. Dr. Meggs responded that there were, and he recommended reading the 2008 RAC report and several PowerPoint presentations that were listed on the RAC website. Dr. Korn asked if this plan builds on past studies. Dr. O'Callaghan responded that indeed the recommendations did build on studies that are described in the 2008 RAC report.

Dr. Korn suggested that this information should be stated clearly in this section of the strategic plan since he did not believe the readers would do a library search to find this information regarding prior studies. Mr. Hardie also agreed with this point.

Dr. Buja said that when he looked at these sets of bullets in this section of the plan, he remarked that it seemed that the animal researchers were telling him that GWI is a chronic degenerative neuropathologic condition that has inflammatory components and triggered systemic autonomic system and immunologic dysfunction. He said that it was implied that there was nothing else to study. Dr. Barlow responded that she did not think that was what they were saying, but instead that they were trying to say that to date within the research that has been conducted, there seemed to be a very strong link to what we researchers see clinically. She clarified that it did not mean there were not additional things that could be studied. Dr. Barlow added that it was important to emphasize in the animal models section how much progress has been made to date with these studies. She remarked that genetics and environmental exposures are exciting areas that need to come through in this report and should be studied further. Chairman Binns responded that instead of telling people what to study, it would be better to give them the background that might intrigue them to study those areas.

Dr. Korn also suggested that it would be wonderful if somebody in ORD or somebody in the working groups could prepare a short list of major advancements in the understanding of GWI that veterans as well as politicians could read. Chairman Binns indicated that one section had

prepared that kind of an overview.

Dr. Buja suggested moving on to the next section (section 5.7) which was improved coordination and communication with federal partners and researchers in the private sector (Appendix B, document 1). Dr. White said that this section tried to summarize means by which the research could be efficiently coordinated and integrated as it moved forward in a flexible fashion. She commented that there was a lot of yellow highlighting in this section. She believed the most important piece to this section was adapting the GWISC to oversee the research effort. This group would hold monthly virtual meetings in which they would process new findings, what was funded, and oversee the project in real time with mechanisms for rapid funding of pilot studies. She added that the section began with a description of all the players, so the second goal involved interagency coordination of funding and scientific initiatives. She moved on to the next goal which was scientific communication of results and hypotheses to the scientific community. The next goal was ongoing dialogue and communication with Gulf War veterans and the last goal was to enhance managing and coordinating communications to treat veterans with GWI.

Dr. Buja asked if the Steering Committee were to conduct monthly tele-meetings, would every funded researcher be included on the tele-meetings? He also asked how topics would be chosen for the meetings. Dr. White responded that her group proposed that the GWISC would have representatives for each meeting and there would be a regular rotation of investigators that attended. Dr. White added that if one group of people looked at the progress that was going on, they could increase the efficiency on how research was done by connecting researchers as well.

Dr. Steele then added that one of the issues that had been raised about the Gulf War research program at VA was that people do studies but no one builds on the results of other people's studies. Dr. White added that the recommendation asked for people like Dr. Jaeger and Dr. Kalasinsky to be involved, so VA would be hearing about all the studies going on.

Dr. Buja then asked Dr. Grosser to talk about his model technique to look at how metabolic pathways were related. Dr. Grosser started with his presentation to give an example for how one might monitor success of any research program. He researched on pubmed on the internet for multiple terms relating to GWI. Based on his research, there had been 353 papers published over the years since the Gulf War. He explained that the annual rate of Gulf War research based on the number of papers was decreasing. He suggested that one could use this tool to see how the VA funding actually impacted the field.

Dr. Buja said that when he saw this he postulated that one of the goals should be to develop mechanisms to increase the connectivity among researchers. LTC Knox commented that the support of federal funding in the report matched the support of federal funding based on his presentation. Dr. Laine found this interesting and it showed there was research activity but that everyone had to remember that some of the most cited papers in research are papers that had been retracted. Dr. Grosser added that this again was not the solution to everything, but a way to monitor success of a research program.

Dr. Kupersmith responded that this was the kind of thing they were interested in and that there had been a lot of criticism about the way they evaluated research by bibliometrics. He added that nobody had really determined a better way to determine the impact of the funded research.

Dr. Jaeger added that with bibliometric analysis, you find out there are more bibliometric methods that have been proposed than you ever thought existed, and you have to be judicious in selecting them.

Dr. Steele noticed that with Dr. Grosser's presentation, that after a certain point, collaborations did not continue to rise. She advised that it would be great if VA could fund a center, where there were people from different backgrounds working together. Dr. Sullivan and Dr. Barlow agreed that it was very important for people to collaborate in such a multi-disciplinary research field as GWI.

Dr. Buja then suggested that the group move to the translation section (section 5.8) of the draft report for discussion (Appendix B, document 1). Dr. Buja said that this section stated that when Gulf War research results showed a successful treatment, each successful treatment would be translated into clinical practice by some mechanism. Dr. Kupersmith responded that Congress appropriates money to each department, and added that VA should discuss ways to collaborate with the CDMRP and to then find appropriate mechanisms to implement better methods for collaboration.

Dr. Buja announced a short break in the meeting. When the break was complete, he introduced the last section of the strategic plan report for discussion, which was the conclusion section. The first paragraph of the conclusion indicated that the first working plan for research on what was then referred to as "Gulf War veterans illnesses" was published in 1995-96. The general progress in science since the first plan included mapping the human genome, advances in medical imaging, and advances in medical informatics and electronic health information. Examples of advances made by GW researchers included a survey of 30,000 Gulf War and Gulf War era veterans showing that 35% of the Gulf War veterans suffer from multisystem illness, compared to 10% of veterans who were not deployed. Imaging studies have shown alterations in brain structure in Gulf War veterans exposed to sarin/cyclosarin, and treatment studies showed that CPAP partially relieved GWI symptoms. Dr. Buja concluded by saying that the summary list of scientific advances should be used to make an appendix to the strategic plan document. Dr. Steele responded that there were several places in the plan with several paragraphs that could be put together to make a summary of recent advances in GW research.

Chairman Binns said that he thought it would take some reworking to accomplish the goal that Dr. Korn and Dr. Barlow were discussing. Dr. Buja suggested an appendix in the back of the report which could have a list of topic categories. Dr. Barlow agreed with that idea and added that the report would also need something that included real data that investigators could feel and see.

Dr. O'Callaghan agreed with Dr. Barlow and said that the introduction could be placed before the objectives for each section in the draft strategic plan. Dr. Barlow added that it should be summarized in a way so that it captured what was believed to be the most important advances in the last 15 years of GW research.

Dr. Jaeger then mentioned that the Journal of Rehabilitation Research and Development had a summary for the veterans before each article, which proved to be successful for everyone to understand the topic.

Dr. Buja said that they would take all these ideas into consideration when finalizing the draft strategic plan. He then moved onto the next paragraph of the conclusion section which indicated that there was potential to build on progress that had been made to date. He emphasized that the overall goal of the plan was to improve the health and well-being of Gulf War veterans and to utilize emerging knowledge to prevent similar war-related illnesses in the future. The final paragraph indicated a lot more work needed to be done, and the plan would be reviewed annually by the Gulf War Steering committee, RAC and the NRAC. He concluded by saying that the major points made today would go into a revision that would be sent out to everyone to see what had been changed and this would be done in time to have the document ready for presentation to the NRAC for their next meeting.

Mr. Hardie also suggested that before the discussion was finished, that the group may want to look at the title of the draft report as well. He suggested that the word illness should be added to the title. Dr. Steele then suggested that maybe surveillance should also be added in the strategic plan title. Chairman Binns said that he did not know if this was necessary because it had always been called the Gulf War Strategic Plan and perhaps it should stay that way.

Dr. Steele said since the first research goals were established by VA for Gulf War health problems, there had not been much actually accomplished with regard to accomplishing that research within VA. She was anxious that even though VA had now stated the new research goals, the plan may not follow through on accomplishing them.

Mr. Hardie asked if it would be helpful to go back to the subcommittees to insure implementation of the research goals in their sections or to create an implementation subcommittee for the strategic plan. Dr. Buja responded by saying that Mr. Hardie's suggestion made sense but that implementation of the strategic plan wasn't up to the subcommittees. Dr. Buja said that he hoped that having gone this far in a cooperative effort, that the steering committee could provide a vehicle for interim feedback of the research goals. He also asked if the group wanted to add the word "illness" to the strategic plan title, and the group responded that they did.

Chairman Binns concluded that it had been a productive meeting that provided a lot of insight. He added that the more people and stakeholders that were involved in this planning, the better chance there was of succeeding and he appreciated the participation of the ORD and OPH representatives. He thanked everyone that participated in the working groups as well. He then called for statements from members of the audience for the public comments section of the meeting.

Public Comments

Jim Bunker, executive director of the National Gulf War Resource Center, introduced himself and provided a reflection of his experience during the Gulf War. He spoke on behalf of the veteran community and said that they are tired of research that did not address their illnesses, but wanted research focusing on treatment. He said that when he met with Dr. Lea Steele in the mid-1990's, he was on two crutches and could barely use his hand. He said that detoxification and getting off most of the medications VA prescribed to him had helped him greatly. He commented that treatment therapy that would address the symptoms of veterans is one of the main issues that studies and research needs to be focused on. He finished off saying that he and other veterans just want treatment, and a better quality of life.

Major (retired) Denise Nichols then shared her experience. She indicated that now veterans are getting more and more diagnosed and that they do not understand how all their health problems connect. She stated that the surveillance program was terribly important, and it needed to be a high priority. Major Nichols then recounted the death of a fellow GW veteran named Michael Woods, who had died on Veterans Day. She commented that he had been a leader in the community, leading a march all the way from Florida to Washington, D.C. and she stated that he would be sorely missed.

She also stressed that she did not believe that he had gotten the proper medical care and if he had been getting proper preventative care, that he may still be alive. She stressed that the group should be cognizant of those GW veterans who have died. She then stated that many sick Gulf War veterans are not able to work or make a living and that Gulf War veterans are going in to their doctor and are getting no answers and this needed to be addressed.

She also remarked that veterans put their claims in for service-connection and they are also shuffled around. She then stated that these veterans are sick and asked the Committee not to make it all about research. She also stated that, "As a nurse, you have got to look at the whole picture. Michael Woods died of colon cancer. How many deaths from colon cancer did we have? Go get the death data right now. We have a smaller number of deaths, and it shouldn't take us a year to get that data of what the cause of death was, their age, and what unit, and we shouldn't have to wait five years for an update."

Chairman Binns thanked them both for their comments.

Dr. Baraniuk, of Georgetown University, had a quick comment. He believed that the committees had a bad public visibility. He stated that he had healthy veterans come in for studies that believed that GWI did not exist. He believed that there was a large amount of education that needed to get out to ill veterans with GWI, to the healthy veterans and to the current staff who were trained at the VA. Dr. Baraniuk mentioned that he works on the chronic fatigue working group for the NIH and one thing they have done every year for the past five years was to have an investigators meeting and they have been very good at bringing the top funded investigators together each year. He suggested having a forum where investigators can get together for GW illness research as well.

Retired Major Denise Nichols had one last comment by stating that web conferencing would be

helpful for these meetings to increase transparency and to activate the scientific community. She also believed that it would help Gulf War veterans to see the committee as it functions.

Chairman Binns thanked everyone, and adjourned the meeting for the day.

DAY 2

The February 1, 2012 meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses (hereinafter referred to as the Committee) was held in Room 1143 at the Lafayette Building, 811 Vermont Avenue, NW, Washington, D.C.

Welcome, Introductions & Opening Remarks

Mr. James Binns, Committee Chair

Dr. Kimberly Sullivan, Committee Associate Scientific Director

Chairman Binns called the meeting to order at 8:30 a.m. He introduced Dr. Victor Kalasinsky from ORD to discuss the VA research program.

Update of VA Gulf War Research Funding

Dr. Victor Kalasinsky, VA ORD

Dr. Kalasinsky gave a brief overview of the research portfolio in Gulf War research (Appendix A-Presentation 1). He updated the Committee regarding the total number of completed and ongoing funded Gulf War projects through the VA. He stated that some of this research was funded by the DOD and that VA had many excellent researchers. He added that the ORD was in the process of evaluating proposals that were received through the latest RFA's. Dr. Kalasinsky stated that one of the issues that he and Dr. Jaeger would have to deal with within VA and the Gulf War research in particular, was getting people excited about doing Gulf War research.

Dr. Grosser asked Dr. Kalasinsky how many of the submitted studies during this cycle did he think he would be able to fund? Dr. Kalasinsky responded that he didn't have a funding line that was determined by the number of proposals and that he didn't have a fixed amount of money that they would spend regardless of quality of the proposal. Dr. Grosser responded saying that to raise interest, publishing the funding line would be extremely important and may increase interest in which Dr. Kalasinsky said that he could do that in the future.

Dr. Sullivan asked Dr. Kalasinsky if he could tell her about this regional transcranial magnetic stimulation (RTMS) study that recently got funded. Dr. Kalasinsky responded that Dr. Wes Ashford in Palo Alto was funded for this study.

Dr. Sullivan then asked that in regards to funding, whether investigators were encouraged to resubmit their grants?

Dr. Jaeger commented that when he originally came to National Institute of Disability and Rehabilitation Research, he was charged with studying the peer reviewed practice of comparable federal agencies and making recommendations to improve that agency to review peer review

process. He had given an example where there were several cases that investigators would try resubmitting more times than the three that was allowed. Because the VA is an intramural research program, the peer review process in the VA goes farther than any other agency in terms of getting feedback to investigators and trying to get them to improve their proposals and resubmit them.

Dr. Sullivan said that she understood his point but that sometimes there were significant delays in getting reviews back to the investigators before the time of the next resubmission date. Dr. Sullivan then asked that if investigators got a score that was a reasonable score, but there were some issues with their proposal, if they could be funded within that cycle if they were allowed to fix their proposal to address those issues? She stated that this could improve the number of proposals funded since Dr. Kalasinsky had just stated that 1 investigator got funded out of 10 proposals in the last funding cycle.

Dr. Jaeger said that they had something called “conditional approval.” He said that the mechanism was there that if the panel agreed that there was a good proposal but it had some flaws, that the panel would offer suggestions to fix the flaws. Dr. Sullivan suggested that this be encouraged in the future when possible. Dr. Jaeger added that everything is peer reviewed so if a reviewer says it isn’t good science, then we can’t fund it.

Chairman Binns added that VA’s overall program may be liberal and excellent but historically there had been a problem that the merit review groups who had reviewed Gulf War proposals because they did not include sufficient numbers of people who understood the research area. He also stated that more than a year went by before there was any grant review feedback on proposals that were submitted in the fall of 2010 and that this was a significant problem.

Dr. Jaeger said that in the panels he ran at the VA, if they had a proposal where an applicant felt that their review did not have the proper reviewers, he would go and search for additional reviewers to come in on the resubmission but he couldn’t say that happened in every single panel.

Chairman Binns encouraged that from this point forward ORD lean toward everything that could be done to encourage VA researchers to submit grants to the Gulf War research program.

Dr. Jaeger added that he and Dr. Kalasinsky would be able to devote more time to identifying a pool of reviewers that may broaden research funding more.

Dr. Golomb said that she felt that the history of the VA training guide for clinicians treating GW veterans had done a great deal of damage to the GW research program had contributed to the perception among people at the VA that GW research wasn’t a legitimate field. She suggested that the enthusiasm problem might be substantially addressed by having some form of new training that allowed researchers in other fields to see that this is the domain for their areas of interest.

Dr. Barlow agreed with Dr. Golomb and thought that relevant research could draw in more researchers.

Dr. Jaeger said that this was where the pilot mechanisms of funding could come in because preliminary data generally wasn't necessarily for this funding mechanisms and he thought the pilot mechanism was the closest thing the VA had to fund new GW researchers in the next couple of funding cycles.

Dr. Barlow said that the only issue with that, especially if ORD was trying to push more therapeutic interventions and translational work, that the \$100,000 in pilot funds would not be enough funding for these types of studies and increasing the budgets for these grants should be considered.

Dr. Steele clarified her prior comments by saying that the Committee had been talking about the need for pilot funds for treatment trials specifically, because data needed to be developed around potentially good treatments and then launch them into larger trials. She said that it seemed that ORD needed to issue separate RFAs for pilots, and that hadn't been done for treatment trials.

Dr. Jaeger asked Dr. Steele how she felt about the plan to fund pilot studies and then if a certain effect size was achieved then it could be considered for funding for a bigger trial. Dr. Steele responded saying that she did not think it should be a cut and dry rule, and that it should depend on the sample size of the trial. She added that other agencies are offering development trials, pilot trials, and small evaluation studies for early studies of treatments and there are a lot of models to look at how to put it all together.

Dr. Barlow suggested that VA consider what the effect size would need to be to go on to a larger treatment trial because if a pilot study is not statistically significant, you won't get funded for the next round since people in clinical research are driven by statistical significance. She said that effect size is a much more realistic way of looking at what you should do in the next trial.

Dr. Golomb asked what if the study was effective for overall health, but not something else, then the fact that it had a good effect size in one domain could invalidate it from future consideration.

Chairman Binns then said that approximately half of the CDMRP funded projects are submitted by VA researchers and asked why the VA wasn't funding their further follow-up research? He added that since CDMRP is the one that funds them, it reduces the number of projects that can be funded from the population of GW researchers in general.

Dr. Jaeger said that VA investigators are always encouraged to leverage their intramural position to get NSF, NIH and DoD funding. He added that in a previous agency, he tried an interagency experiment where identical proposals were submitted to the NIH and to the VA and the results of those peer-reviewed analyses were very comparable.

Dr. Steele responded saying that there weren't enough investigators submitting good proposals to VA and that there were good investigators making good proposals to CDMRP from VA so there was a problem.

Dr. Jaeger responded saying that peer reviewed systems are different, and at CDMRP they have a scientific review and they have a relevance review and that VA didn't have a relevance review.

Dr. Steele responded saying that the RFA's from VA from last year stated that there was a relevance review, and from the language it suggested that there would continue to be one.

Dr. Jaeger said that he has not been involved directly with the Gulf War peer review panel so he would have to double check that in the RFAs.

Dr. Grosser asked Dr. Kalasinsky if he could talk about the grant proposals themselves. He asked what the length of the proposals was particularly because these things influenced the readability of the proposal for the reviewers and also the threshold for submitting the proposal. Dr. Kalasinsky responded that the grant proposal research plans were generally in the range of 10-12 pages. Dr. Grosser also asked if there was a significance section similar to NIH proposals, in which Dr. Kalasinsky responded that there was.

Dr. Barlow asked that for the VA-funded investigators that did not send in resubmissions for their proposals, if it was because the reviewers suggested that it wasn't a viable hypothesis or line of inquiry that they were submitting, or was it because they didn't feel that they could get funded through the VA.

Dr. Kalasinsky said that he didn't know the answer to her question but that there were some slight differences in the way money could be spent. He had been told that the review process was essentially no different from their perspective.

Dr. Sullivan responded by saying that she knew of two people who had taken virtually identical grant proposals that were sent to the VA Gulf War program and they did not get funded. They then sent them to the CDMRP and were funded by the CDMRP Gulf War program. Dr. Jaeger said that different agencies have their peer review systems and different panels review things differently.

Dr. Buja had a question which was if the Gulf War proposals compete with other types of proposals and are reviewed by reviewers with general expertise, then he could see them getting torpedoed very easily.

Dr. Kalasinsky said that there is a specific Gulf War review panel, so there were subject matter experts in the different fields in the different proposals and also folks who had done Gulf War research on the panels. Dr. Buja followed up by saying that there was still a problem in spite of the special expertise. Dr. Kalasinsky said that maybe there wasn't a problem, but that his office would be sure to structure the panel correctly in the future.

Dr. Steele asked Dr. Kalasinsky how much funding that the one recently funded Gulf War project was funded for. Dr. Kalasinsky responded that it was funded for about a million dollars.

Chairman Binns requested a list of the names and the amount of funding of the VA Gulf War portfolio for future meetings. Dr. Kalasinsky responded that he would have one to distribute for the next Committee meeting.

Mr. Hardie asked when the VA intended to start using consumer reviewers as the CDMRP does. Dr. Jaeger responded saying that he did not have an answer, but he would go back to VA central office and ask about this possibility.

Mr. Hardie said that as a longtime reviewer of CDMRP, having a consumer reviewer could have a profound difference on the evaluation of a proposal. He also had a comment regarding the lack of recently funded proposals through VA. He added that if VA planned to solve GWI, their funding performance was not doing it now considering that only one study had been funded in the past 18 months.

Chairman Binns closed with the statement that Dr. Jaeger and Dr. Kalasinsky are the hope of the future for VA Gulf War research. He said that they have been dramatically successful in managing participation of ORD in the strategic plan process. He encouraged them to continue this forward leaning work and that he knew that they have challenges working within the VA agency. He welcomed them and hoped that they could make a difference in the future for Gulf War research.

Dr. Jaeger followed up by saying that thus far, they had made a difference considering there was no strategic plan a year ago and that now there was one.

Mr. Hardie followed by stating that he thought that it would be very helpful to determine whether treatments are particularly helpful or not for Gulf War veterans and whether they were specific or general treatments. But he was unclear how it was known that mindfulness therapy was going to help veterans to combat pain.

He explained that in coping with a particular symptom of Gulf War illness where one has to consider what the difference was between a pharmacological therapy for pain versus a mindfulness intervention for pain that it appeared that they weren't very specific for the treatment of GWI but rather general treatments for Gulf War related symptoms. He added that polypharmacy therapies may also be an issue in treating Gulf War veterans as well.

Dr. Barlow followed Mr. Hardie's comment by saying that what she had deduced was that it was frustrating for veterans that these were the only kinds of treatments that were currently being looked at rather than additional types of treatments. It seemed to her that veterans were wondering if there was an aggressive or more novel method that should also be on this list of treatments so that the veterans have a chance to have a substantial increase in the quality of their lives.

Dr. Jaeger followed with a comment that anyone that was interested could visit the NIH reporter website and sort by agency to see what VA has recently funded. Dr. Steele asked how many proposals that ORD had received in the last round of RFA's, in which he responded that there were ten proposals. Dr. Sullivan asked in the recent grant reviews, how many had come in, in which Dr. Jaeger responded that there were sixteen proposals recently submitted.

Chairman Binns thanked everyone for the discussion, and asked Dr. Sullivan to introduce the next speaker, Dr. Mian Li.

Washington WRIISC Research Update

Dr. Mian Li, WRIISC Center

Dr. Li presented his research on the evaluation of chronic autonomic symptoms in Gulf War veterans with unexplained fatigue (Appendix A-Presentation 2). He explained that the peripheral autonomic nervous system consisted of afferent and efferent components and that neurotoxins may preferentially affect the small nerve fiber. He explained that in his study, he used heart rate variability testing in his patient population of Gulf War veterans. The testing involved subjects blowing air into a tube with 40-meters of pressure, and holding it for 15 seconds. Then it was released in order to get a tachycardia response. In another part of his research, his patients had fatigue, weakness, and myalgias. In these patients, the Valsalva ratio was very low. He explained that the Valsalva ratio was probably low because the two groups were not healthy, or because the two groups had a high resting heart rate. In his study, there were 17 people in the symptomatic group and 13 controls. He performed a tilt table test with all of the study participants. He explained that the symptomatic group had a maximum heart rate that was much higher than the controls. In his sample of the symptomatic and control groups, he did not see much difference, even after repeating the tests.

He remarked that to diagnose peripheral neuropathy, sensory symptoms, motor symptoms, and autonomic symptoms had to be integrated. Then, quantitative sensory testing and nerve conduction studies were performed.

He commented that the qualitative sensory axonal reflex testing (QSART) was useful for small fiber neuropathy testing. He said that with QSART, you get a reflex increase and activation of other branches to the sweat gland, because of a sympathetic response. Dr. Li reported that in his 17 patients, there were two that had small fiber neuropathy and that by definition, if a patient had small fiber neuropathy then they did not have large fiber neuropathy.

Dr. Golomb asked what the doctors used for the myopathy. Dr. Li responded that he used needle EMT. He proceeded to talk about QSART and how it worked with sensory testing and heart rate variability. He said that the two came together in the Compound Autonomic Severity Score or CASS. The sudomotor subscore was 3 points, the adrenergic subscore was 4 points, and the cardiovagal subscore was 3 points. His results showed that there was increased motor neuropathy in the sick group.

He concluded that self-reported unexplained neurological symptoms could be confirmed on a battery of objective autonomic testing in selected GW veterans and that objective parameters on autonomic testing may be useful in guiding the treatment of selected multi-symptom illnesses in an appropriate clinical context.

Chairman Binns thanked Dr. Li and asked if there are any treatments that he found effective in correcting autonomic imbalance. Dr. Li responded that there are several FDA-approved medications that he uses to treat large fiber neuropathy and fibromyalgia.

Dr. O'Callaghan asked Dr. Li if his various subcategories in the CASS scoring system had been cross-validated with actual neuropathology from peripheral nerve biopsies, and Dr. Li indicated that they had been cross-validated by at Mayo Clinic researcher.

Dr. Grosser was interested in how Dr. Li selected controls and ill patients. Dr. Li said that recruitment was done by Dr. Han Kang, who had sent the questionnaires and identified the sample population. Dr. Grosser suggested to Dr. Li that he should demonstrate between the groups that there was no difference in metabolic syndrome.

Chairman Binns thanked Dr. Li, and asked Dr. Sullivan to introduce the next speaker, Dr. Julia Golier from the Bronx VA.

The HPA Axis in Gulf War Veterans

Dr. Julia Golier, Bronx VA

Dr. Golier presented her research regarding the Hypothalamic-Pituitary-Adrenal (HPA) axis in Gulf War veterans. Her initial rationale for looking at HPA axis was because it is involved in the stress response and overlapped with many functions of chronic multisymptom illness (CMI). The first study involved the dexamethasone suppression test (DST). Dr. Golier explained in her presentation (Appendix A- Presentation 3) that dexamethasone was an exogenous steroid that mimicked the action of cortisol, and cortisol had negative feedback with adrenocorticotropic hormone (ACTH) and corticotrophin-releasing factor (CRF). She indicated that this was used in clinical neuroendocrinology, and was used in the study of PTSD and depression.

In the first study, the groups were Gulf War veterans with PTSD and major depressive disorder (MDD), Gulf War veterans with PTSD, Gulf War veterans without PTSD or depression, and the non-deployed group. Results showed that Gulf War veterans with no psychiatric disorders had a significantly greater response to DEX compared to the healthy non-deployed group. Results also showed that Gulf War veterans had significantly greater cortisol suppression than the non-deployed group. She remarked that Gulf War veterans who reported pyridostigmine bromide ingestion, had higher DST suppression, but combat and other exposures were not association with DST. She concluded that with Gulf War veterans, there seemed to be a link with deployment and pyridostigmine bromide, but not PTSD.

She also undertook a study of cortisol and ACTH levels over a 24 hour time period in Gulf War veterans with PTSD, Gulf War veterans without PTSD and non-deployed veterans. The results showed that there was no group difference in cortisol levels and there was also no change in the overall diurnal variation. Gulf War veterans without PTSD or without any psychiatric disorder had significantly lower ACTH levels.

Dr. Steele asked if the subjects were well or just did not have PTSD. Dr. Golier responded that they had no PTSD and no other major medical illnesses. However, it was possible that they could have had other medical symptoms.

She raised the possibility that there may have been a deployment effect on ACTH levels. She then said that if you controlled for the effect of PTSD overall, deployment was associated with significantly reduced ACTH levels at virtually every point along the 24-hour cycle, and although the numbers were small, there was an association with both deployment and pyridostigmine bromide exposure.

She explained that one possibility that the ACTH levels were so much lower in the deployed group could have been because of the dexamethasone suppression test. The system was overly

sensitive to the feedback of cortisol, so it may be that there was so much feedback lowering ACTH. To account for the sensitivity of the test, she also used the metyrapone stimulation test. Metyrapone is a medication that inhibits 11-beta hydroxylase, which is an enzyme that converts deoxycortisol into cortisol. She said that after it is administered, an acute increase in deoxycortisol and acute decrease in cortisol occurs, and that frees the HPA axis from the inhibitory effect of cortisol.

She indicated that another way to assess central drive to HPA axis is to look at the CRF stimulation. CRF is a hypothalamic peptide that stimulates the release of ACTH from the pituitary, and then, in turn, cortisol from the adrenal glands. The study looked at Vietnam veterans, Gulf War veterans, and OIF/OEF veterans were given a fairly low dose of CRF. The results showed that there was a very clear difference with both of the deployed groups being than the non-exposed groups. There was a significant group by era interaction, and while admittedly the sample sizes got very small, the Gulf War group behaved in a way that is completely different from the other two groups.

She said that looking at the environmental exposures, pyridostigmine bromide was associated with a peak change in ACTH. The cortisol response to the CRF stimulation test showed that the two deployed groups showed a greater cortisol response, but in this case, there was no difference by era.

She said that she also looked lower down in the axis and directly stimulated using ACTH. The cortisol response to ACTH was very similar to what she saw with the cortisol response to CRF and that the two deployed groups had a greater cortisol response, but this also did not differ by era.

Overall, she explained that there was dysregulation at multiple points in the axis and a very dynamic sensitized response to stress, but somehow basal cortisol levels were very well maintained and it seemed that there were elements that were nonspecific to the Gulf and some that were quite specific. She suggested the possibility that there was a reduced drive centrally to the HPA axis in Gulf War veterans. She did not know the exact mechanism but she said this would make it distinctly different from any other stress-related disorder.

She remarked that currently, she was in the final stage of a crossover study of mifepristone in Gulf War veterans with CMI. Mifepristone is a glucocorticoid receptor antagonist, and therefore diminished the enhanced data feedback that she described on the HPA axis. She explained that a compensatory increase in ACTH and cortisol production occurs but the mechanism is not entirely known. In this study she was looking at cognitive functioning, mental health, and whether or not baseline HPA axis activity would predict a response. The study was blind, so she did not know what the results would be yet.

She concluded that it seemed that CMI or Gulf War deployment puts people at risk for secondary medical complications, and that the HPA axis dysregulation is in some way involved. She would also be looking at cortisol and its metabolites to understand cortisol metabolism in this study. She hoped to understand what the metabolic profile is associated with CMI and whether it is or is not linked to the HPA axis.

Dr. Barlow responded that she had looked at a lot of clinical trial data with mifepristone and that

it is important to note that mifepristone was not an effective treatment for major depressive disorder, and that maybe that was an important thing to think about when Dr. Golier's data came out. She added that Dr. Golier may need to reconsider the matrix battery that she had used, and may need to reconsider how the data was analyzed.

Dr. Golier responded that these were fairly standard tests that were administered in her mifepristone study. Dr. Barlow responded that she was not indicating that Dr. Golier chose the wrong test, but in regards to practicality, it had not been able to pick up signals when they were sometimes there and that there were newer test batteries that may be more effective.

Dr. Sullivan agreed with Dr. Barlow and said that it was incredibly important to pick sensitive cognitive tasks especially when you are looking at something like a treatment outcome and whether it is effective or not. Dr. Barlow added that the matrix battery was really set up for psychotic, psychiatric diseases, schizophrenia, psychotic depression, and was not a primary fundamental issue in Gulf War illness.

Dr. Steele asked Dr. Golier if she saw potential for there to be some predictive value for GWI case status in relation to the dexamethasone suppression test. Dr. Golier said that she would know once she finished her study, but it looked as if everyone was affected.

Dr. Barlow said that it was interesting that it seemed that there was nothing wrong with the veterans at baseline, but when they were stressed, the phenotypes separated out. She suggested that going forward within the strategic plan, the group should encourage outside researchers to look at aspects that ask the system to function at a higher level rather than just looking at baseline measurements. Dr. Golier agreed with Dr. Barlow's point.

Mr. Hardie asked Dr. Golier if she asked questions related to Khamisiyah and potential sarin exposures in her study participants. Dr. Golomb replied that she believed that every veteran exposed to the Khamisiyah detonations were exposed to low-level sarin. Mr. Hardie indicated that this was a difficult issue because there were veterans that may not know what chemical warfare agents they had been exposed to. Dr. Golier responded that with the top-down approach, one of the things that would be very helpful would be an agreed upon way of assessing exposure information in GW veterans.

Chairman Binns thanked Dr. Golier, and asked Dr. Sullivan to introduce the next speaker. Dr. Sullivan introduced Dr. James Baraniuk of Georgetown University.

CDMRP Studies at Georgetown: GWI subtypes

Dr. James Baraniuk, Georgetown University

Dr. Baraniuk discussed his research on exercise in GWI (Appendix A, Presentation 4). He stated that the purpose of this study was to use exercise to induce exercise-induced exhaustion in Gulf War veterans with GWI compared to veterans from the Gulf War era without GWI. For recruitment, he had subjects complete an on-line questionnaire. Then his study team performed a complete history and physical examination to try to confirm their diagnosis and to identify what other exacerbating illnesses they may have. He stated that a lot of blood work was done and he

conducted dolorimetry, which was pressure testing to induce pain. He also performed isometric handgrip and acoustic rhinometry testing with his study participants. On the first day of the study protocol, he had veterans perform an fMRI test and an N-Back test to assess working memory. Then the participants would perform a bicycle ergometry exercise stressor test.

On the second day, the participants performed the second exercise again, but then in reverse order, by doing the bloodwork first, followed by the dolorimetry thumb pressure, isometrics, and then the bicycle exercise. Within about an hour of ending the exercise, the participants would repeat the fMRI and Dr. Baraniuk would look for differences on the N-Back test of working memory.

Dr. Sullivan noted Dr. Baraniuk's slide regarding Gulf War veteran symptoms and asked if more of the subjects got headaches than the controls and Dr. Baraniuk responded that they did. He remarked that on day 3 of the study protocol, that he found that 80 percent of the patients had typical migraines whether with or without auras. To measure how severe fatigue was in his subjects, Dr. Baraniuk scored them on a grading scale from zero to four.

In his initial group of 600 participants, the controls had fatigue levels of zero, 1 and 2 while those with CFS had scores of 3 or 4. He explained that the underlying hypothesis driving the work was that the central sensitization is the underlying mechanism that was responsible for the changes in cellular responses and neurological responses throughout the body. He explained that central sensitization meant that you apply stimulus with the result of a larger effect and this was where the primary synapse between the peripheral pain-carrying nerves and the secondary ascending spinothalamic fibers occurred. He stated that this was also the location of intense regulation involving microglial cells, A-beta fibers, and other modifying influences.

He explained that with dolorimetry, they take the 16 or 18 general tender points of the body and press on it with the dolorimeter, to measure the average pressure that produced pain. His results showed that females had an average pain shifted towards the lower kilogram range compared to males, but there was a very striking shift of both chronic fatigue and GWI to the bottom compared to the healthy controls. He stated that overall, exercise was good as a way to appreciate pain, but his data was still under evaluation.

In regards to the N-back test, in the healthy veterans, their score for a 2-back was about 80 percent, and there was no change with exercise. Among the Gulf War veterans with chronic fatigue, their responses were significantly lower than those of people who had GWI only. He indicated that the second major finding was that he could not tell the difference between the two groups at baseline however, after the two exercise tests, one group increased their 2-back scores, and therefore had improved cognition.

Dr. Steele asked Dr. Baraniuk, if he saw anything like that in GWI only. Dr. Baraniuk responded that it turned out to be a very small component of the people that he had recruited. Dr. Golomb asked if he identified any other markers that correlated with who would show their decrements vs. increments. Dr. Baraniuk responded that that data was still under analysis. Dr. Golomb then asked what outcomes that he was looking at. Dr. Baraniuk explained that he was looking at the changes in their central sensitization, changes in their exercise performance, their post-exercise fatigue levels, and mRNA changes in their leukocytes.

Chairman Binns thanked Dr. Baraniuk for his presentation, and moved onto the committee discussion.

Committee Discussion

Chairman Binns stated that the group would be going through a discussion of the material from the prior day's meeting. He commented that then the Committee would have a chance to discuss the recommendations related to the successor to the draft strategic plan report, which was first discussed at the last meeting and that the group had assembled some draft recommendations (Appendix B, document 2). He concluded that the plan needed to be refined into an operational plan. He also noted that many parts of the plan were subject to the execution of different offices of ORD, which had not yet signed off on the plan, and whose signoff was required for those portions of the strategic plan.

He then said that the draft recommendation provided that the RAC Committee would recommend the adoption of the draft strategic plan with the caveat that outside advisors be consulted in the preparation of the operational plan, such as through an expanded Gulf War Steering Committee, or other mechanisms that could be developed, and that the content of the operational plan be presented to the Committee and the NRAC for review and advice before final decisions were made.

The second recommendation was that the other VA offices adopt the strategic plan and operational plan, so that the result would be a single VA-wide research program.

He summarized that the Committee had recommended the addition of soliciting pilot studies of treatments through RFAs, and that a treatment research center or other directed process should be established to supplement the identification and initiation of promising treatment pilot studies. The committee also recommended that VA would no longer characterize as Gulf War research projects outside the two areas of inquiry recommended by the Institute of Medicine 2010 report, continued surveillance of Gulf War veterans and a renewed research program to better identify and treat multisymptom illness. As an example, VA should not include CSP501A, the ALS brain bank in their funding levels for GWI research. The Committee also recommended that funding for the Million Veteran Program should be categorized as Gulf War research only for the studies directly related to Gulf War multisymptom illness research. Chairman Binns also recommended that ORD reiterate the amount of yearly spending for the Gulf War related studies.

Chairman Binns stated that the last recommendation was that VA needed a centralized research effort both administratively within VA's staff and the leadership of the program, and in the conduct of such a program in order to make it of maximum effectiveness. He also added that within ORD, the administration of the program should be centralized under the Director of Deployment Health. He also added that research studies funded through general RFAs and reviewed by the Gulf War Merit Review Panel should be made up of individuals with expertise in Gulf War research. He also suggested that the \$15 million being expended by VA for Gulf War research should include the money being spent on the national Gulf War veteran survey.

His last comment was that he felt that the strategic plan would remedy the deficiencies in the current Gulf War research program through VA, particularly with respect to the low levels of current research funding for multisymptom illness research.

Dr. Golomb had a comment regarding a sentence in the draft recommendations that regarding the "for research only for study of Gulf War Multisymptom Illness." She wondered if maybe they should add the word "specifically" after "for research only." She wondered if it should be emphasized that the Gulf War Merit Review Panel should have research relevant expertise in Gulf War research.

LTC Knox expressed her frustration that even though the RAC is considered an advisory committee, most of the time the advice of the Committee was not taken and she urged VA to implement the strategic plan as soon as possible.

Dr. Steele had some additional comments in regards to Chairman Binns' caveats. She believed that there were certain caveats specific to funding issues, and funding of studies wasn't covered by the strategic plan, therefore she indicated that they should be moved to the funding recommendation. She also suggested changing the language regarding that the strategic plan was not really an operational plan. Chairman Binns suggested that maybe it could be reworded to "recognizing that the operational plan will be the actionable plan and that historically, advisory plans have frequently been identified in the past, but not translated into action."

Dr. Steele also added that the strategic plan needed to reflect a sense of urgency to identify treatments for sick veterans after so many years. Chairman Binns indicated that it was in the plan and that he felt that one of the good things about the plan was that it did reflect a sense of urgency.

Dr. Barlow added that in regards to the HPA axis and the new data coming from Georgetown University, she hoped that Dr. Jaeger and Dr. Kalasinsky could convey that message internally to the VA clinical researchers about the new and interesting research coming out. She added that the plan needed more punch because there was some truly phenomenal science coming out, that could be meaningful for multiple types of Gulf War studies going forward.

Mr. Hardie remarked that he hoped that people from the VA and from other agencies understood the frustration that he expressed was just not his own, but also anger and frustration that he gets daily from other Gulf War veterans. He found great hope in the research findings that continued to be presented before this committee and the research proposals that he saw coming through the CDMRP,. He added that he found it heartbreaking when he saw that almost \$31 million of research proposals was making it all the way to the final round of the CDMRP this year, but only \$6.94 million was able to be distributed. He expressed that if this strategic plan was implemented, it has potential of helping to solve many issues.

Dr. Jaeger said that he and Dr. Kalasinsky would indeed carry all this back to central office. Dr. Kalasinsky added that the things discussed during the two day meeting were all things they were currently working on.

Dr. Schneiderman expressed his disappointment in the RAC recommendation to halt the national survey of Gulf War veterans that his office has been planning. He remarked that he saw the

potential to harm veterans by not being able to carry out the survey on the schedule that OPH currently had in place.

Dr. Golomb stated that the concern was that if the survey did not include the information that enabled proper identification of affected Gulf War veterans, then they may not get meaningful data in the end and that would ultimately be worse than slowing down the start date.

Dr. Schneiderman responded that he had a history of working with this panel, and on the information about symptoms, about illness, they had contributed greatly to the survey, and the survey was now fine.

Dr. Steele responded that they understood his position but in the first round of reviewing the survey, the Committee saw many deficits in the symptom inventory, and they were concerned about the data they were collecting. She added that the Committee members were not saying to slow down the data collection but to just show the Committee the data that OPH would be collecting.

Chairman Binns responded that it was difficult to read from the response that OPH sent to the Committee whether or not there were changes made to the Gulf War survey or not.

Dr. Sullivan said that it was her understanding based on Dr. Schneiderman's written response to the Committee that there were a lot of things that OPH considered changing in regard to the RAC recommendations but that it did not ever say what exactly they would or would not change, so the Committee assumed that they would get a copy back to be able to see what was and what was not changed in the next version of the survey. Dr. Steele remarked that the Committee just wanted the right data collected and that if the third survey was going to be modeled after the second survey, then that would be problematic. She explained the problem with this strategy for the survey was that the second survey did not capture the most important data for determining multisymptom illness and that the third survey would also fail to collect this data as well. Dr. Barlow agreed with Dr. Steele's point and added that it would be a larger travesty to move forward with a study that in the end did not produce the kind of results that would be most useful.

Dr. Meggs asked Dr. Schneiderman if the survey was revised, and if so why they were not able to see it. Dr. Schneiderman responded that they were waiting for OMB's approval.

Mr. Hardie then said to Dr. Schneiderman that he would encourage this strong message from the Committee to be carried back to OPH and that the presentations that had been made by OPH in the last two days had done nothing to build trust between the Committee and his office. Mr. Hardie recognized that Dr. Schneiderman may have been very limited in what he could or could not say, but that trust has been broken with the OPH. He added that the Committee had no idea what the survey looked like after the recommendations were sent to OPH, and he remarked that the scientists on this committee had great reason to be concerned as to whether those recommendations were followed or not.

Chairman Binns proceeded to the remainder of the Committee discussion with Dr. Sullivan's presentation regarding Committee recommendations for the Gulf War pre-911 report (Appendix A-Presentation 4).

Dr. Sullivan started the discussion about the Gulf War pre-9/11 report recommendations. She said that the Committee was given a briefing at a prior meeting for this newly revised report that provided what the Committee thought was a substantial advance in publicly available VA data, and built upon the former GWVIS report. She stated that the overall recommendation was to enhance the future additions of what the Committee thought was a very important report by improving how the subgroups were defined in the report.

Another recommendation regarding the GW Pre-911 report was to create a non-deployed-group for comparison to Gulf War veterans and Dr. Sullivan said that it would be helpful to include data on the number of claims filed and the number of veterans service-connected for diagnosed medical conditions. She explained that another recommendation for the Pre-911 report was to report overall totals for all tables reported to clarify what the data was actually meant to convey. She explained that this would help to reduce logical impossibilities in data reporting such as incorrectly stated ages for Gulf War veterans. Dr. Sullivan said that the Committee also thought that including stakeholders familiar with this cohort and draft versions of the report could also be helpful in making sure that all the data reported was correct and accurately described. A further recommendation was that in addition to the Gulf War Desert Storm subgroup (which is currently provided in the report) that two other subgroups should be included, which would include the Desert Shield only (i.e., those entering the theater after August of '90, and departed prior to January of '91), and post-Desert Shield only (entered the theater between February 20th, '91, and July of '91 regardless of departure date). Another group that was recommended to also be included was a suitable Gulf War era non-deployed comparison group. Dr. Sullivan stated that the Committee also recommended that a continuation of providing data for the special focus groups including Khamisiyah and Al Jubayl, would also be important to include in future editions of the Gulf War Pre-911 report.

Dr. Sullivan also indicated that some Committee members felt that the title of the report should be changed as well.

Dr. Steele had a comment that one of the big problems with that data report was that the Gulf War deployed group included Desert Storm veterans for an additional year when it should have been a one-year period and not two years.

Dr. Sullivan then said that the next recommendation was that all costs should be listed in the report as well. Mortality statistics were also recommended to be included for all cohorts and for all categories in the report. The recommendations also included identifying uses of VHA and VBA by ICD-9 codes particularly for the 8800 series (for undiagnosed illness).

A further recommendation was that data should be included that showed undiagnosed illness claims approved for all cohorts and that data be included that showed claims for all cohorts for the nine new presumptive rare endemic diseases. Dr. Steele and Mr. Hardie both agreed with these recommendations for the Gulf War Pre-911 report.

Chairman Binns then introduced the public comments.

Public Comments

Paul Sullivan, a Gulf War veteran, thanked the Committee for their work on the strategic plan. He commented that he supported VA's interim rule that was published at the end of December

2011, extending the period for the manifestation of symptoms that were created by the 1994 undiagnosed illness law and the amendments that were passed in 2000 and in subsequent years. He remarked that he supported ending the manifestation period all together because science showed that the manifestation takes a decade or longer to occur in many veterans. He said that the second reason he supported the elimination of the manifestation period is that the Gulf War actually continues to the present and there are still deployed service members into the Southwest Asia war zone. He supported expanding the definition of Southwest Asia to include other nations nearby such as Turkey because the same toxins that GW veterans were exposed to are present in the current war zones. He indicated that VA needs to make sure that veterans are also included under the benefits law that is 38 CFR 3.317. He commented its importance because if science comes up with treatments for Gulf War veterans, the Gulf War veterans would not be able to get those treatments unless they were service connected by the Veterans Benefits Administration. He concluded that the benefits rules have to be modified in order to meet the new and emerging science and he hoped that the Committee and VA officials took that into consideration.

Retired Major Denise Nichols first thanked everyone on the Committee for their hard work. She indicated that the veteran community feels abandonment and they just want treatment and answers, not compensation. She indicated that this was not a normal research advisory committee and that this was started by an Act of Congress, and the president when he signed it. She lastly stated that the Committee and VA could do better.

The last comment was made by Mr. Jim Bunker regarding further research with ill Gulf War veterans. He indicated that Dr. Li has been finding that there is a problem in the small fiber neuropathy in veterans. When Mr. Bunker looked up research on neuropathy issues, he found that the research stopped back in the 1990's. He added that Dr. Li's studies needed to be looked into further and that there needed to be further studies that looked at what these issues were.

Chairman Binns offered his thanks for the public comments and noted that the VA Chief of Staff, Mr. John Gingrich, was personally in the Gulf War and commanded Jim Bunker. He said that the Secretary's office has done a lot more than anyone else, to recognize the health problems of Gulf War veterans and yet the Office of Public Health was about to send out a survey, in which the main result would be to infuriate 30,000 Gulf War veterans. He concluded the meeting by saying that he has been chairman of the Committee for 10 years, and shares in the responsibility that research has not found treatment answers for Gulf War veterans, but that those answers can and will be found.