Research Advisory Committee on Gulf War Veterans' Illnesses

June 27-28 2011, Committee Meeting Minutes

Department of Veterans' Affairs
Washington, DC

Research Advisory Committee on Gulf War Veterans' Illnesses
Boston University School of Public Health
715 Albany Street, T4W, Boston, MA 02118
Phone: 617-414-1392, Fax: 617-638-4857

I hereby certify the following minutes as being an accurate record of what transpired at the June 27-28, 2011 meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses.

_____

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

Table of Contents

Attendance Record

Members of the Committee
James Binns, Chairman
Roberta White, Scientific Director
Dedra Buchwald
* Beatrice Golomb
Anthony Hardie
Marguerite Knox
William Meggs
James O'Callaghan
Lea Steele
Adam Such

Committee Staff
Kimberly Sullivan
Sadie Richards

Designated Federal Officer
Bill Goldberg

Guest Speakers
Gordon Broderick
Maximilian Buja
Nancy Klimas
Polly Matzinger
Scott Panter
Joseph Salvatore

* present for June 27th only

Table of Contents

Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses
June 27-28, 2011

Department of Veteran Affairs, 810 Vermont Avenue, Washington, DC

Agenda
Monday, June 27, 2011

8:00 – 8:30	**Informal gathering, coffee**	
8:30 – 8:35	**Welcome, introductory remarks**	**Mr. Jim Binns, Chairman Res Adv Cmte Gulf War Illnesses**
8:35 – 9:30	**Altered immune functions in Gulf War illness and potential therapies**	**Dr. Nancy Klimas Miami VA Medical Center**
9:30 -10:30	**From Cytokines to Cells to Gene Expression: An Integrative Approach to the Study of Gulf War illness**	**Dr. Gordon Broderick University of Alberta**
10:30 – 10:45	**Break**	
10:45 – 11:45	**Intranasal administration of toxicants and therapeutics**	**Dr. Scott Panter San Diego VA Medical Center**
11:45 – 12:45	**Lunch**	
12:45 – 1:30	**Co-Enzyme Q-10 treatment trial of Gulf War illness**	**Dr. Beatrice Golomb Res Adv Cmte Gulf War Illnesses**
1:30 – 2:15	**Gulf War Pre-911 Report overview**	**Mr. Joseph Salvatore VA Office of Policy and Planning**
2:15 – 2:30	**Break**	
2:30 – 3:30	**The Danger Model of innate immune system activation**	**Dr. Polly Matzinger National Institutes of Health, NIAID**
3:30 – 4:15	**Federal Advisory Committee Ethics Training**	**Mr. Jonathan Gurland**
4:15 – 5:00	**Public comment**	

Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses
June 28, 2011

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

Agenda
Tuesday, June 28, 2011

8:00 – 8:30	**Informal gathering, coffee**	
8:30 - 9:30	**Update of VA Gulf War Cooperative Studies**	**Dr. Timothy O'Leary** **VA Office of Research and development**
	Update of VA Gulf War research funding	**Dr. William Goldberg** **VA Office of Research and development**
9:30 – 10:15	**Committee Discussion: VA Gulf War Comprehensive Research Strategy**	**Mr. Jim Binns, Chairman** **Dr. Roberta White, Scientific Director** **Res Adv Cmte Gulf War Illnesses**
10:15 – 10:30	**Break**	
10:30 – 11:45	**Presentation of minutes of the April 20 meeting of the GW Steering Committee**	**Dr. Maximilian Buja, Chairman** **Gulf War Steering Committee**
	Presentation of the Strategic Plan for VA Gulf War Research	**Dr. Maximilian Buja, Chairman** **Gulf War Steering Committee**
11:45 – 12:30	**Committee Discussion: VA Gulf War Comprehensive Research Strategy**	**Mr. Jim Binns, Chairman** **Dr. Roberta White, Scientific Director** **Res Adv Cmte Gulf War Illnesses**
12:30 – 12:45	**Public comment**	
12:45	**Adjourn**	

DAY 1

The June 27, 2011 meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses (hereinafter referred to as the Committee) was held in Room 230 at the Department of Veterans' Affairs, 810 Vermont Avenue, NW, Washington, D.C.

Welcome, Introductions & Opening Remarks

Mr. James Binns, Committee Chairman
Dr. Kimberly Sullivan, Committee Associate Scientific Director

Chairman James Binns called the meeting to order at 8:47am. He began by announcing that there was an article in the current day's USA Today highlighting a clinical trial conducted by Committee member Dr. Beatrice Golomb which found that ill Gulf War Veterans who were administered a particular antioxidant experienced modest health benefits. Chairman Binns noted that this indicated that the Institute of Medicine (IOM) was correct in stating that research, done right, could lead to treatments and hopefully cures for Gulf War Illness (GWI). He then asked Dr. Kimberly Sullivan to introduce the first speakers.

Dr. Sullivan, Associate Scientific Director of the Committee, introduced Drs. Nancy Klimas and Gordon Broderick.

Altered Immune Function in Gulf War Illness and Potential Therapies

Dr. Nancy Klimas, Miami VA Medical Center

Dr. Klimas introduced the research she and Dr. Broderick have collaborated on to investigate immune system functioning in Gulf War Illness, followed by Dr. Broderick's presentation of the systems biology component of their research. Drs. Klimas and Broderick then presented together on their future research and treatment suggestions.

Dr. Klimas first presented a model of Gulf War Illness as a deviation from homeostasis involving imbalances across the interactive immune, autonomic and endocrine systems in the body. Dr. Klimas' presentation focused on immune abnormalities seen in GWI, including immune activation, poor cytotoxic cell function, cytokine regulatory disruptions and abnormalities of neuropeptide Y (NPY) and cytokines that interface with autonomic, endocrine, and neurologic mediators (see Appendix A – Presentation 1). Dr. Klimas asserted that many of the mediators seen were strong enough to be considered as biomarkers for GWI, and that immune activation, proinflammatory cytokines and factors that promote this steady state of activation and inflammation were reasonable targets for intervention. She also noted that one of her current ongoing studies involving exercise intervention among 37 ill Gulf War veterans suggested that there were differences between males and females, though larger cohorts were needed to draw conclusions. Dr. Klimas then gave an overview of gene-environment interactions before introducing Dr. Broderick.

From Cytokines to Cells to Gene Expression: An Integrative Approach to the Study of Gulf War Illness

Dr. Gordon Broderick, University of Alberta

Dr. Broderick presented on the genomics and systems biology component of the GWI research that he and Dr. Klimas are conducting (See Appendix A – Presentation 2). He explained that the approach he was using to explore the data involved looking not only at parts that might be defective but also how those parts were integrated and regulated in respect to one another. Dr. Broderick stated that his current research was using biomarkers in the blood to take a snapshot which could be used to look at the wiring (or connected networks) regulating the body's immune, autonomic and endocrine function. He explained that assessing these networks on the genomic and proteomic scale involved employing statistical tools to quantify the degree of difference between networks in a healthy state versus an illness state. Dr. Broderick said his next step was to qualify how the networks differed. In a recent study initially involving 10 ill Gulf War veterans and 11 healthy veteran controls, Dr. Broderick found that the networks differed between these populations at rest, at peak exercise effort and post-exercise, though the degree and architecture of the differences varied across different stages of the exercise challenge among ill Gulf War veterans. More specifically, networks in ill Gulf War veterans were bigger, not as efficient and not as centrally organized as those of healthy controls. Dr. Broderick also discussed findings regarding specific biomarkers and pathways in this population, including 112 pathways that were differentially active in Gulf War Illness patients versus healthy controls, 89 of which were unique to Gulf War when compared to Chronic Fatigue Syndrome (CFS). The preponderance of these were immune and associated signaling (versus metabolic) pathways.

Drs. Klimas and Broderick then discussed their future research directions and the progress being made toward achieving them (see Appendix A – Presentation 3). Before doing so, Dr. Klimas addressed a concern that Dr. Dedra Buchwald, a member of the Committee, had raised about their number of study participants. Dr. Klimas stated that they had been funded for and would ultimately include 60 ill Gulf War veterans, 85 healthy Gulf War era veteran controls and 45 individuals with CFS in their study. Drs. Klimas and Broderick then explained that the first goal for the future was to complete the dataset needed for the comprehensive systems biology analysis of GWI.

Dr. Bill Meggs, a member of the Committee, asked Dr. Klimas about her statement that some of the associations were so strong that they could serve as a biomarker for GWI. He specifically wanted to know what she would recommend be tested pre- and post-treatment in any clinical trials involving ill Gulf War veterans.

Dr. Klimas replied that there was debate over whether to break the overall population into sub-groups based on biomarkers in the sub-population and clinical treatments being tested. She said that when she was trying to improve the function of the immune system she would select a population based on natural killer (NK) cell function, for instance, and that would be a good biomarker and outcome variable. She noted that she would add to that outcome variable another marker of immune function, such as an inflammatory cytokine biomarker (e.g. IL5). She added that her laboratory would soon be utilizing a custom nanostring of 300 different probes (identified by Dr. Broderick) that could be analyzed without PCR or other amplification.

Dr. Beatrice Golomb, a member of the Committee, expressed interest in the differences and overlaps between CFS and GWI cases and asked whether Dr. Klimas had looked at the subset of ill Gulf War veterans in her study who met the criteria for CFS and evaluated what their profiles looked like. Dr. Klimas replied that all of her GWI subjects met the CFS criteria, which was a criteria of their study. Dr. Golomb then asked for clarification regarding whether all of the Gulf War patients were CFS patients. Dr. Klimas replied that technically they were, but that metabolically they weren't.

Dr. Buchwald then remarked that in any disease like GWI or CFS, she believes the most important outcome is how people feel. Therefore, Dr. Buchwald expressed her belief that the important biomarkers are those that directly relate to how an individual feels. Dr. Meggs followed up on Dr. Buchwald's comment by asking if any biomarkers correlated with symptoms in CFS. Dr. Buchwald replied that it was controversial, and not the point she was trying to make. She added that, given the small number of participants, she would encourage Drs. Klimas and Broderick to present their research as highly speculative. Dr. Buchwald also emphasized that the environmental component of disease was a critical piece of the picture that she had not heard Dr. Klimas or Dr. Broderick address, and that well-designed studies should involve hundreds of participants, ideally matched twins. She commented that one very powerful option for methylation studies would be to conduct a study of even just 10 pairs of monozygotic twins discordant for Gulf War. Speaking from her experience, Dr. Buchwald remarked that network modeling studies could only be observational, but not speak directly to causation.

Dr. James O'Callaghan, a member of the Committee, asked if Drs. Klimas or Broderick had thought about utilizing knockout mice to study the disrupted networks of specific gene disruptions.

Dr. Broderick stated that the pathway modeling he was conducting had been biochemically validated and that he was trying to move toward causal models. He remarked that animal studies and time-course studies would allow for causation to be inferred. Dr. Broderick agreed with Dr. Buchwald's assertion that a good biomarker would be directly related to symptomology, and that it would also be able to be manipulated and thus an entry point for a pharmaceutical intervention (e.g. enzymes and proteins, rather than genes).

Dr. Roberta White, the Committee's Scientific Director, expressed her excitement over the exploratory work Drs. Klimas and Broderick were conducting. She stated that she was not surprised that GWI looked different from CFS, particularly because she had difficulty getting her GWI veterans to meet standard CFS criteria. She supported the addition of all components that would further understanding of causation. Dr. White suggested using their methodology to look at individuals with known exposures to the toxicants that were present in the Persian Gulf War theatre. Some potential populations she mentioned included Dr. Freya Kamel's agricultural workers and other occupational groups with similar exposures to pesticides and other chemicals that were present in theatre. Dr. White stated that if Drs. Klimas and Broderick were interested in pursuing studies in those populations she would like to work together to gain access to them.

Dr. Klimas welcomed such collaborations, and mentioned that her research group was developing a biobank of exceedingly well-described patients, and that she would be happy to

share samples if there was something that Dr. White wanted to look at in serum or plasma that had not yet been measured by Dr. Klimas' team. Dr. White then stated that she would put Dr. Klimas in touch with Dr. Kamel.

Dr. Golomb then recommended that Drs. Klimas and Broderick look at ill Gulf War veterans who did not meet the criteria for CFS.

Dr. Steele, a member of the Committee, then asked if Dr. Klimas was conducting exposure assessments as part of her research. Dr. Klimas replied that she was probably not doing it as well as she would like, but that if Dr. Steele had an instrument to recommend she would be happy to add it to the panel and recontact the participants in order to gather that data.

Mr. Anthony Hardie, a Gulf War veteran on the Committee, thanked Drs. Klimas and Broderick for their research and congratulated them for receiving consortia funding through the Congressionally Directed Medical Research Program (CDMRP), noting that he hoped the message would be carried forward to Congress that CDMRP funding for Gulf War research was non-duplicative of VA funding. He then requested that they provide a brief layman's description of their findings and the implications for veterans with regard to symptom improvement or possible treatments. Dr. Klimas replied that the conclusion of her prepared presentation addressed these issues, which she then proceeded to discuss. She remarked that her research showed that even small exertions of the type that most individuals carry out daily were sufficient to trigger debilitating symptoms in veterans with Gulf War Illness. Mr. Hardie remarked that, as an ill Gulf War veteran, he completely agreed, and he then thanked Dr. Klimas for understanding. Dr. Klimas replied that she was a clinician with 30 hours per week in patient contact, which she felt gave her a tremendous sense of what ill Gulf War veterans were going through.

Dr. Klimas then presented examples of two drugs that block the IL1 receptor, one of which she was currently seeking funding to investigate in a phase one study. She explained that she and Dr. Broderick were also brainstorming ways to improve cell and HPA axis functioning. Dr. Klimas then thanked the Miami VA Medical Center for their support of her work, noting that an upcoming project would involve her participation in telehealth video clinics whereby ill Gulf War veterans around the country could, with their local providers, video conference with Dr. Klimas in order to train these providers in appropriate approaches to care.

Chairman Binns then asked Dr. Klimas to clarify the relationship between her research and the VA Strategic Plan. Specifically, Chariman Binns asked whether Dr. Klimas' work was currently supported by CSP-585. At this point Dr. Goldberg, the Committee's Designated Federal Officer, interjected to state that CSP-585 was on hold. Dr. Klimas replied that she believed there was a preliminary study to determine the feasibility of CSP-585, but that she could speak best to the rational for why such a study would be useful (as opposed to whether or not is was going to be done). Chairman Binns remarked that to him Dr. Klimas' work seemed to be putting meat on the bones of what the IOM meant in their report of the previous year when it identified genomics as an area of importance for Gulf War Illness research. Dr. Klimas replied that this characterization seemed fair to her. Chairman Binns then stated that this was what he would like to see in a strategic plan. Dr. Klimas then commented that genome-wide association studies (GWAS) had

the ability to inform the model because a systems biological approach could be applied to GWAS. She added that one of the limiting factors was budget restraints. Chairman Binns then echoed what Mr. Hardie had said about the VA and CDMRP funding not being duplicative, and Dr. Klimas concurred. Chairman Binns then asked whether Dr. Klimas' proposal could be made to the VA (instead of CDMRP). Dr. Klimas responded that most of her protocols could have been submitted to either the VA or CDMRP. She commented that she would like to gather all of the investigators together to learn what each other were doing. Lastly, Dr. Klimas expressed her support for the funding of more than one consortium.

Chairman Binns then thanked Drs. Klimas and Broderick for their work. He called for a 15 minute break and reconvened the meeting at 11:07am, at which point Dr. Sullivan introduced Dr. Scott Panter.

Intranasal Administration of Toxicants and Therapeutics

Dr. S. Scott Panter, San Diego VA Medical Center

Dr. Panter began his presentation by describing the route by which intranasally administered drugs enter the brain and central nervous system (CNS), bypassing the blood brain barrier which typically prevents many substances from passing through (Appendix A – Presentation 4). Dr. Panter then described the rat model of stroke that his laboratory has used to study neuroprotection by intranasal administration of deferoxamine (DFO). Dr. Panter's research in this model has shown that pre- and post-stroke treatment with intranasal DFO significantly reduced infarct size. Dr. Panter added that other research suggests that intranasal administration of DFO may be useful in the treatment of certain CNS disorders. Dr. Panter also recently received funding to administer human embryonic stem cells to the brains of pigs. Past research has demonstrated that stem cell therapy shows promise for the treatment of Parkinson's Disease (PD), and Dr. Panter expressed his optimism for similar approaches to studying and deriving therapies for Gulf War Illness. In addition to intranasal therapeutics, Dr. Panter has researched toxicant exposure via inhalation. One such chemical of relevance to Gulf War exposures that Dr. Panter has studied is DEET. During his presentation, Dr. Panter also recommended utilizing the good twin registries in the Scandanavian countries to study Gulf War Illness.

Dr. Sullivan thanked Dr. Panter for his presentation and asked if he had looked at the specific pathways by which the intranasally administered agents were able to get into the brain. Dr. Panter replied that extensive work had been done using fluorescent or radio-labeled compounds, and that effects of intranasal administration occurred rapidly, within 15-20 minutes.

Dr. Golomb then asked what approach was used to target the upper third of the nasal passage in humans. Dr. Panter replied that a nasal sprayer known as OptiNose could be used for this purpose.

Dr. Golomb then asked whether Dr. Panter had considered extending his research to include settings such as repeated exposures to landscape gardeners and others who use organophosphorous pesticides (OPs), herbicides, and termite control chemicals. Dr. Panter replied that this issue was of concern, even at VA hospitals. He stated that his philosophy was that if a chemical could be smelled, one should breathe through his or her mouth, as this would

reduce transfer of the chemical to the blood supply. Dr. Panter then talked about the use of intranasal insulin in patients with Alzheimer's Disease (AD), which resulted in increased brain concentrations of insulin, accompanied by increased memory acquisition and recall, but which didn't affect peripheral blood glucose levels or exert any systemic effects. Dr. Panter then spoke about the antioxidant properties of DFO.

Dr. Steele then expressed her appreciation for Dr. Panter's research, remarking that it was an intranasal study of sarin that had revealed persistent neurotoxic effects of low-dose exposure. She expressed interest in seeing studies of inhalation of formulations of DEET used in the Gulf War, as well as permethrin. Dr. Panter agreed, but remarked that chemical formulations often change over time.

Dr. Sullivan then commented that she had done a study with Gulf War pesticide applicators (such as those tasked with spraying prisoners of war with the delousing agent lindane) who reported that they had not been supplied with enough replacement filters for their protective suits during the war, which resulted in a high degree of intranasal exposure for these GW veterans.

Dr. Panter stated that, when asked by the Department of Defense (DoD) what could be done to reduce exposure, he recommended the use of nose plugs like those that swimmers wear. Dr. Sullivan agreed that this was a good idea.

Dr. Sullivan then remarked that other investigators had recommended pig models for studies of OP exposure. Dr. Panter replied that the pig brain was similar to the human brain.

Dr. Sullivan also commented on the preliminary studies conducted by Dr. William Frey and Dr. Suzanne Craft which, as Dr. Panter had mentioned, suggested that intranasal insulin administration could improve memory in AD and be targeted to exert its effects only in the CNS. She expressed her belief that this type of approach would be worth considering for ill Gulf War veterans reporting cognitive issues.

Dr. O'Callaghan then asked if Dr. Panter had conducted any of his stroke model studies in aged rats. Dr. Panter replied that he would be looking at male vs. female and young vs. old rats. Dr. O'Callaghan commented that he was aware of recent research showing that the pathobiology of aged rats suffering from ischemic stroke was different from that modeled in younger rats. Dr. Panter replied that he had found differences in alcohol metabolism in old vs. young rats, and would be interested to look at both age and sex differences in stroke.

Mr. Hardie thanked Dr. Panter for his work and remarked that many ill Gulf War veterans (including himself) suffered from chronic sinusitis. Mr. Hardie explained that he had undergone several surgeries to relieve those symptoms, but that those procedures resulted in increased chemical sensitivities – another symptom common to many ill Gulf War veterans. Mr. Hardie acknowledged that this was an anecdote, but urged Dr. Panter and other clinicians seeing Gulf War patients to consider that veterans with Gulf War Illness might suffer from sinus issues and/or be more sensitive to chemicals than the general population, which Mr. Hardie pointed out could skew results of studies looking at uptake and effects of intranasally administered substances.

Dr. Steele thanked Mr. Hardie for his comment, and recalled a previous presentation to the Committee given by Dr. Johnnye Lewis, from the University of New Mexico, about intranasally administered depleted uranium (DU). In mice with inflamed nasal passages, low dose exposures to DU resulted in much deeper penetration and inflammation of the brain not seen in DU exposed mice without nasal inflammation. She asked if Dr. Panter was familiar with similar context-specific effects of intranasally-administered substances. Dr. Panter replied that he did not think that had been well studied, but that he would expect to see a lot of individual variability depending upon the prior life experiences of each individual. Dr. Panter acknowledged that people in the Gulf War (and people in OIF and OEF) have modified physiologies such that they are hyper-alert, high cortisol levels, dehydrated, hyperthermic, and sleep-deprived. He said that these characteristics had to be considered in animal model studies, though replicating them could be difficult.

Chairman Binns then asked what effect stem cell treatment had in the animals with chemically-induced PD. Dr. Panter replied that the signs of PD disappeared after the animals were treated with bone marrow derived stem cells, and that the necrosis occurring in the brain tissue of these animals before treatment did not occur after stem cell treatment.

Dr. Klimas then asked how the stem cells entered the brain, since they were not small. Dr. Panter replied that cells and nucleic acids could actually passively enter the brain. He added that he believed human embryonic stem cells held much more potential than the promising bone marrow derived stem cells, but that federal funding for embryonic stem cell research had, until recently, been restricted. Dr. Panter stated that he had recently received substantial funding from the California Institute of Regenerative Medicine to conduct some of this research.

Chairman Binns and Dr. Sullivan then thanked Dr. Panter. Dr. Sullivan then stated that Dr. Matzinger's presentation would occur later that afternoon. Chairman Binns then called for a lunch break.

Chairman Binns called the Committee to order again at 1:20pm with an introduction of the next speaker, Dr. Beatrice Golomb, a member of the Committee who began researching Gulf War Illness in 1996. Chairman Binns remarked that Dr. Golomb's study demonstrates the truth of the IOM's report from the previous year, which stated that proper research could likely lead to treatments and hopefully preventions.

Co-Enzyme Q-10 Treatment Trial of Gulf War Illness

Dr. Beatrice Golomb, Research Advisory Committee on Gulf War Veterans' Illnesses

Dr. Golomb began by thanking the CDMRP and DoD, then introduced her talk on the double-blind randomized pilot study of Coenzyme Q10 (CoQ10) she had conducted in ill Gulf War Veterans (See Appendix A – Presentation 5). Dr. Golomb explained that many Gulf War exposures were known triggers of oxidative stress, thereby contributing to mitochondrial dysfunction, energetic decline, cell death and associated symptoms. Dr. Golomb then explained that CoQ10 is the primary fat-soluble antioxidant made by the human body which has been

shown to (variably) reduce symptoms associated with various mitochondrial dysfunctions (which are often characterized by ongoing production of oxidative stress after exposures have passed). Though the study was small, and findings must be viewed as provisional, Dr. Golomb's results suggest that CoQ10 at doses of 100mg per day can produce modest but material benefits across numerous symptoms and domains of relevance to Gulf War veterans.

During Dr. Golomb's presentation, Dr. Klimas asked if she had used ubiquinol (the non-reduced form of CoQ10) or ubiquinone (the reduced form of CoQ10). Dr. Golomb replied that she had used ubiquinone, which had been shown to alleviate some symptoms of mitochondrial dysfunction in previous studies. She later added that the brand she chose was known to have very high bioavailability and no additives that could offset results. Mr. Hardie then asked Dr. Golomb to clarify how the two forms differed from each other. Dr. Golomb replied that ubiquinone was a form of CoQ10 which had been reduced (as opposed to oxidized), whereas ubiquinol was not reduced. Mr. Hardie then asked what forms were contained in bottles of CoQ10 that were not labeled ubiquinone or ubiquinol. Dr. Golomb replied that if the packaging did not specify that it was ubiquinol then it was likely ubiquinone.

At the conclusion of her presentation, Dr. Meggs asked if Dr. Golomb had used the standard 10cm visual analog scale for the symptom scores. Dr. Golomb replied that she had not. Rather, participants rated their symptom severity on a scale of 1 to 10 in order to adjust for baseline as a contributor to change. She explained that participants also rated each symptom as "much worse" or "somewhat worse" or "about the same" or "somewhat better" or "much better."

Dr. Steele expressed her gratitude for Dr. Golomb's research, remarking that she thought Dr. Golomb's approach could help inform others' research as well. She stated that one benefit of pilot studies such as Dr. Golomb's was the determination of whether some treatments help some people, not just averaging the response across all patients in the study. Dr. Steele then asked Dr. Golomb if she had noticed or in her analysis identified subgroups who seemed to respond substantially more than the rest of the patients. Dr. Golomb replied that she had extensive exposure data, but that the samples will be small to look at a lot of predictors, but that those analyses would be forthcoming. She added that she had recently received data on her participants' malondialdehyde levels (which is a marker of oxidative stress), so she was planning to look at whether patients' oxidative stress levels at the beginning of the study correlated with any findings regarding the effectiveness of CoQ10 treatment. Dr. Steele then asked if Dr. Golomb was able to tell from her analyses thus far whether the effect on symptoms overall driven primarily not because a lot of people got a little benefit but because a few people got a lot of benefit. Dr. Golomb said that she would look into that.

Dr. Sullivan then asked if Dr. Golomb would consider doing a larger study of CoQ10 in Gulf War veterans or would she consider other antioxidants, or perhaps combinations. Dr. Golomb replied that the combination she recommends to ill Gulf War veterans as well as other patients with multisymptom illness is COQ10, starting low and slowly increasing dose to see what works best for each individual. She added that the bioavailability of CoQ10 varies greatly across different brands, and that the formulation she used in her study (with high bioavailability) could not be obtained in the United States, and that mail ordering was complicated. For brands available in the United States (for which Dr. Golomb acknowledged that she has no data), she

recommended Geriformulas. Dr. Golomb then spoke to Dr. Sullivan's question, stating that she had learned a lot from the pilot study and would like to conduct a larger study of CoQ10 in Gulf War veterans.

Dr. Hardie asked Dr. Golomb if she had been funded in 2007, and she confirmed that was correct. He then asked what dose of CoQ10 and frequency of dosage the participants took. Dr. Golomb replied that each participant took 3 pills per day, some of which might have been placebos. Each actual pill of CoQ10 contained 100mg of the drug, so participants who received CoQ10 either got daily doses of 100mg or 300mg.

Dr. Buchwald asked what the washout period was. Dr. Golomb replied that the placebo period (which was also the washout period) was 3 months long. Dr. Buchwald asked why Dr. Golomb had used 2-sided P-statistics. Dr. Golomb replied that she generally felt that 1-sided Ps were sufficient for a pilot study, but that where 2-sided values were significant she showed them. Dr. Buchwald suggested that Dr. Golomb could reanalyze her data to compare the percent of people experiencing a clinical effect to those who did not. Dr. Golomb replied that such an approach was harder to do in a small study like hers. Dr. Buchwald replied that she thought it would be valuable nonetheless. She recommended selecting a clinically significant symptom score threshold (a priori) in order to compare what percent improved and what percent did not improve. Dr. Buchwald also asked whether patients were blinded (whether they knew if they were taking a placebo or CoQ10). Dr. Golomb responded that all participants were told not to take their pills too close to bedtime (insomnia can be a side effect of CoQ10), and if a participant had trouble sleeping the clinicians still remained blind to their categorization until the completion of the study. Dr. Golomb added that, as demonstrated in the unblinding literature, blinding is not likely to be preserved if the treatment is effective at alleviating symptoms. She further discussed findings regarding placebo effect. Dr. Buchwald then commented that a review of the placebo effect in chronic fatigue syndrome suggests that it appears to work differently in CFS. Dr. Buchwald then asked Dr. Golomb to explain her results in light of a large trial conducted in patients with mitochondrial disorders which found no effect of CoQ10. Dr. Golomb replied by reiterating that the effects of CoQ10 were highly variable across various mitochondrial dysfunctional diseases. She did not know what study it was so she said she couldn't comment, adding that quality control of CoQ10 formulation was also pivotally important.

Dr. Steele commented that many of the ill Gulf War veterans suffered from a multiplicity of symptoms, for which they were prescribed a lot of medications. She asked if Dr. Golomb had restricted participation in her pilot study according to medications and how that may have affected the results. Dr. Golomb replied that the participants could not have been on any product containing CoQ10 for at least 4 months prior to the study. She said that she believed some other antioxidants and mitochondrially toxic agents had also been restricted, but that she had wanted the study population to resemble the real world population, so her participants included those on drugs commonly prescribed to ill Gulf War veterans.

Dr. Meggs asked Dr. Golomb what types of medications the participants in her study tended to be on. She replied that information had been collected at every visit and that she would analyze it. He then asked if Dr. Golomb had surveyed the individuals in her study about their perceived

symptom improvements (or lack thereof) following participation in the treatment trial. Dr. Golomb replied that she had not yet analyzed those results because she had been blinded to each individual's status (placebo vs. CoQ10) throughout the study.

Dr. Tilo Grosser, a researcher from the University of Pennsylvania, remarked that although vitamin E had no overall effect on cardiovascular disease, those mechanistic studies which had measured depletion of vitamin E found that individuals supplemented with low levels of vitamin E showed physiological benefits. He encouraged Dr. Golomb to look at whether ill veterans might have depleted stores of particular biomarkers identified in Dr. Golomb's study. Dr. Golomb replied that the problem with CoQ10 was that it is dynamically regulated, such that if one's oxidative stress level goes up so does their CoQ10 level, which can make interpreting CoQ10 levels (and their correlation with oxidative stress) tricky.

LTC Knox then asked Dr. Golomb the name of the other antioxidant which had demonstrated effectiveness in relieving pain. Dr. Golomb replied that it was not necessarily an antioxidant but that she recommended cod liver oil to everybody. She said that many individuals found this effective in the treatment of irritability, pain, mood (though she noted that her proposed study had not yet been funded). She explained that she had separated the components of cod liver oil into vitamin D and omega 3s because reviewers did not like cod liver oil, but Dr. Golomb doesn't believe the two are synonymous. LTC Knox asked Dr. Golomb what brand she recommended and Dr. Golomb said Carlson Norwegian cod liver oil.

Dr. Klimas then remarked that another interesting outcome variable might be CPK, LDH muscle breakdown enzymes (as studied in a recent Japanese study of exercise and fatigue in healthy individuals). Dr. Golomb replied that she had considered doing an exercise trial as part of her original study but that practical and cost barriers prevented her from doing so. She remarked that there was evidence in the statin literature linking high levels of statins, which are supposed to block the metabolic pathway which produces CoQ10, with high levels of CK and massive muscle breakdown. She added that she did see CK as a marker of oxidative stress injury to muscle tissue.

Dr. Sullivan then thanked Dr. Golomb for her presentation. Dr. White then introduced Mr. Joe Salvatore.

Gulf War Era Pre-911 Report Overview

Mr. Joseph Salvatore, VA Office of Policy and Planning

Mr. Salvatore presented an overview of the new reporting mechanism and initial report which includes comprehensive statistics on the utilization of VA benefits and healthcare services by Gulf War Era Veterans (see Appendix A – Presentation 6). Mr. Salvatore suggested that the Pre-911 Report intends to pick up where the Gulf War Veterans Information System (GWVIS) reports left off and report meaningful and accurate integrated data regarding the utilization of VA benefits and healthcare services by Gulf War Era Veterans.

Mr. Jim Bunker, a Gulf War veteran and Executive Director of the National Gulf War Resource Center (NGWRC), asked whether the hypothetical diagnostic code for Gulf War Illness was

included in the system. Mr. Salvatore replied that any diagnostic code in the rating schedule was contained in the database, including undiagnosed illnesses.

Upon being presented with VA healthcare data on the percent increase in various diagnoses for pre-9/11 Gulf War veterans, Mr. Hardie expressed doubt that 108,050 out of the total ~750,000 Gulf War veterans actually had been given diagnoses for endocrine system disorders. Other members of the Committee, including Dr. Steele and Dr. Golomb, also questioned how the number of Gulf War veterans with diagnosed endocrine disorders could be so high. Dr. Golomb suggested that perhaps the "endocrine disorder" classification included some dysfunctions outside the realm of what typically would be considered (i.e. erectile dysfunction or pre-diabetes). Dr. Klimas stated that she believed the number of Gulf War veterans with endocrine disorders could be that high, as it could include all individuals with thyroid problems, diabetes, testosterone recipients. Dr. Steele then asked what percentage of Desert Storm veterans had come into the VA to get any diagnosis, implying that she did not believe it was a very high number. Mr. Salvatore then reviewed the benefits data stating the percent increase in select pre-9/11 service-connected disability categories, which stated that disability connection for endocrine disorder diagnoses increased from 19,360 in FY 2000 to 95, 201 in FY 2009. Mr. Hardie said that he could believe that these numbers were correct. Dr. Sullivan asked if Mr. Salvatore could look at the data, using the ICD-9 codes that are part of the system, and get back to the Committee about that issue. Mr. Salvatore said that he could.

Mr. Hardie then remarked that the data were diluted by extending the time period of service during which individuals could be considered Gulf War veterans from July 31, 1991 for another several months (until 1992) to include "post-Desert Storm" veterans. He stated that this was particularly the case because these post-Desert Storm veterans were the largest group of the three groupings (which also included Desert Storm and Desert Shield). Mr. Salvatore replied that the nature of the database structure would allow him to fine tune his analyses to include just veterans who served during Desert Shield and Desert Storm. Dr. Steele then remarked that doing so would then eliminate a large group of veterans who were still in theatre after the cease-fire on February 28, 1991 through July 1991. In order to avoid combining veterans with different deployment experiences (and potentially different exposures) into a single group, Dr. Steele recommended using the period of August 1990 to August 1991 as the third group (rather than the longer post-Desert Storm grouping that included all of 1991).

Mr. Hardie then expressed his desire for the Committee to make and vote on some formal recommendations to the VA regarding the report at the conclusion of Mr. Salvatore's presentation.

Mr. Salvatore then continued with his presentation. At the conclusion of his presentation he invited the Committee members to contact him, and asked Dr. Goldberg to what channels of communication existed for the Committee to make recommendations. Dr. Goldberg reviewed the process by which the Committee makes formal recommendations, and remarked that few formal recommendations were received from the Committee outside of the reports it issues every four years.

Mr. Salvatore then circulated several copies of his report. Dr. Goldberg asked if the report was posted on the VA website and Mr. Salvatore confirmed that it was.

Dr. Golomb then expressed her appreciation for the work that Mr. Salvatore had done, and his openness to dialogue. Mr. Salvatore said that he welcomed feedback with regard to the time period groupings. He stated that the Integrated Project Team (IPT) had put in a lot of time to ensure that the report structure worked for everyone, and that if the Committee had modifications to suggest he would entertain them.

Dr. Golomb then asked if dates of deployments existed in Mr. Salvatore's database. He said that he would have to go to the DoD for that information.

Mr. Hardie remarked that the frustration of Gulf War veterans had a long history, and that Mr. Salvatore should not take his complaints personally. He explained that he had been working on Gulf War veterans' issues since 1995, and that he was fully connected for being service-disabled. Mr. Hardie then spoke of the many other veterans who were affected in many different ways by their prior military service, and said that he appreciated the data tracking that Mr. Salvatore and his team were doing within the revised system, particularly the ICD-9 tracking. He added that certain terminology (Gulf War or Gulf War era) was preferable over other vocabulary choices (Desert Shield, Desert Storm) to many veterans. Mr. Hardie continued with suggestions that he proposed formalizing with the Committee, including the creation of a report with only Desert Shield and Desert Storm as one component, and that also has those plus the time period through July 31, 1991 because a lot of previous research (including the GWVIS reports) had been based on those time periods, and because exposures that veterans experienced in the Gulf War theater were time-dependent. Mr. Hardie also thanked Dr. Goldberg for urging the Committee to make formal recommendations, which he hoped the Committee would do at the next day's meeting.

Dr. Steele then thanked Mr. Salvatore for assembling the data that the Committee had been requesting for years.

Dr. Sullivan then thanked Mr. Salvatore and called for a 5 minute break. After the break Dr. Sullivan introduced Dr. Polly Matzinger.

The Danger Model of Innate Immune System Activation

Dr. Polly Matzinger, National Institutes of Health

Dr. Matzinger spoke about endogenous immunological danger signals and her theoretical model of the immune system, which posits that the driving force for the immune response is not the recognition of foreign antigen but the recognition of "danger" or alarm signals released by tissue damaged by incoming viruses, bacteria, worms and other pathogens (no presentation available in the Appendix because Dr. Matzinger presented using hand-drawn overhead transparencies). Dr. Matzinger gave examples of biological phenomena which do not fit well in the traditional "self/non-self" model of the immune system, including lactating breast tissue – which produces proteins that the body has never made before that end up in the bloodstream but which do not trigger rejection of that tissue by the maternal body. Other examples Dr. Matzinger discussed in

support of her danger model were lack of the body's rejection of fetuses, surgical transplants, cancer and vaccines (without inclusion of adjuvants).

A member of the audience remarked that Dr. Matzinger's danger model appeared to be describing the classic definition of inflammation, and he asked her what she thought was the difference between inflammation and immunity. Dr. Matzinger replied that she thought that inflammation was the second step in an immune response cascade, where damage, shock or distress was the first step. Dr. Matzinger then mentioned Dr. Carl Hauser's trauma research of systemic immune response syndrome (SIRS), which is triggered by mitochondria released by damaged tissue which then kills about 50 percent of trauma victims. Dr. Matzinger interpreted this phenomenon as indicative of the immune system's reaction to mitochondrial alarm signals (since mitochondria resemble bacteria in many ways).

Dr. Matzinger continued her presentation, discussing various types of alarm signals relevant to the examples she had previously outlined. She spoke about some of the endogenous proteins which are immunostimulatory when "exposed" (which occurs when cells are stressed) including uric acid, ATP, hyaluronic acid breakdown products and lipopolysaccharide.

Dr. Golomb then asked what setting would be considered "exposed" for a normal cholesterol molecule like low-density lipoprotein (LDL), which is up-regulated for the purpose of regulating transport of antioxidants. Dr. Matzinger replied that it depends on how much lipid and what kind of lipid one has in their blood.

Dr. Matzinger proceeded to discuss the example of fetuses, and the fact that the classic immune system model should predict maternal rejection. She expressed doubt over the traditional explanation that fetuses immunosuppress their mothers. Dr. Golomb then pointed out that there is increased risk of certain conditions involving the immune system (such as listeriosis) among pregnant women. Dr. Matzinger acknowledged that there are some parasites that take advantage of the pregnant state. She said she knew little about listeria, but that malaria was another disease that she had looked into because it did not at first appear to fit with her model. However, she said that after studying it further she found that there was a variant of malaria that targets the placenta and for that reason is able to elicit a primary immune response in young pregnant women (who have never been exposed to that variant before). Dr. Matzinger explained that those women who survive create antibodies to that particular variant, and in areas where malaria is endemic all the women have antibodies to that variant but none of the men do.

Dr. Matzinger continued her presentation by discussing transplant rejections and the fact that 25% of the recipients tested did not make an immune response to their mother's cells (though they did respond to their fathers). She explained that a human immune system should respond to any other human except an identical twin. Dr. Golomb then asked if mitochondria might be an alarm signal because it is inherited just from one's mother. Dr. Matzinger said that this was partly the case. She added that mice also exhibit this trait (25% do not respond to cells from their mother). She then continued discussing pregnancy and fetuses in the context of her danger model, noting that fetal development is a process of programmed cell death, and therefore it typically does not involve alarm signals. Thus, the danger model does not predict that fetuses should be rejected.

Dr. Meggs then asked about an RH+ fetus in an RH- mother, and the danger that this could present during birth. Dr. Matzinger said that RH typically becomes a problem in the second pregnancy, not the first. As a result, she explained that doctors give women an antibody to RH during her first pregnancy to cover it up (otherwise the mother could get primed during the "dangerous" or cellular damaging period of birth).

Dr. Matzinger then spoke about transplants, noting that the reason they are so often rejected, according to the danger model, is the trauma caused to the cells of the body by surgeons when they are putting in the transplant. She described a series of experiments using mice that were genetically modified not to have an adaptive immune system whose findings appear to support this hypothesis. These studies were run in her lab by Dr. Colin Anderson, and suggest that if surgeons could do transplants without causing injury to the body the transplants would be accepted by the body and – if left in long enough – would induce tolerance to self and eliminate the need for long-term administration of immunosuppressant drugs in transplant recipients.

Dr. Steele asked if there could be another way to induce tolerance to the future transplant by injecting something from the donor to the recipient prior to the transplant which didn't cause tissue damage. Dr. Matzinger replied that David Sachs and Megan Sykes were currently conducting trials in mice using stem cells, which can induce tolerance over time if administered without tissue damage.

Dr. Matzinger then discussed why the immune system does not reject tumors. According to the danger model tumors are not rejected because it is not inherently dangerous (no alarm signals trigger the immune system until most of the immune cells that are able to combat the tumor have been wiped out). Dr. Matzinger then described a case in which Steve Rosenberg at the NIH cultivated these tumor fighting cells (known as tumor infiltrating lymphocytes), which he then infused back into the cancer patient from which they were collected. Dr. Matzinger stated that this process was done twice, with reduction in tumor size following each round. However, Dr. Matzinger noted that the patient had died after Dr. Rosenberg stopped repeating the procedure. She said that Dr. Rosenberg had not continued the series of treatments because he based his practice on the classic model of the immune system, and as such he believed that the immune response would be maintained because of the presence of the non-self tumor antigens. Dr. Matzinger explained that her danger model framed things differently, in that an alarm signal was necessary for a maintained response, and in these treatments Dr. Matzinger did not believe that the alarm signal was maintained, thus the tumor would regrow after the first and second cycle. She added that Dr. Rosenberg had mentioned in a recent talk that he had successfully eradicated cancer in two patients which he treated with three (rather than two) rounds of this approach. Dr. Matzinger expressed her belief that the failure of many tumor vaccines might not be that they were ineffective but rather that they were not being used correctly (and that repeated administration of some of them might be effective).

Dr. Matzinger then concluded her presentation with a discussion of autoimmunity. She stated that she believes there are 5 categories of autoimmunity, and that there is something is wrong with the immune response in only one of them. These include an unknown infection (e.g. Lyme disease), a cross-reaction with an environmental antigen (e.g. rheumatic fever), "bad death" (cell

death involving alarm signals) which can be caused by toxicants, genetic mutations, etc., "really bad death" (e.g. heavy metal poisoning and scleroderma) and misplaced immune responses (e.g. celiac disease).

Dr. Golomb remarked on immune responses induced by metals and adjuvants, including aluminum. Dr. Matzinger said she was not familiar with immune responses to aluminum. Dr. Golomb then recommended work by Girardi and France on macrophagic myofasciitis and Schoenfeld's research on autoimmune syndromes induced by adjuvants. Dr. Matzinger replied by making the point that immune responses occur under conditions of continued alarm signaling (not just a one-time turning on of the immune response). She felt it was possible that an autoimmune response could be triggered by a major dose of some toxic substance and then maintained by the minor doses of various toxicants present in our daily lives (such as pesticides, chemicals in consumer products).

Mr. Hardie then asked about the impact of radiation or radiomimetic agents (such as mustard gas). Dr. Matzinger said that it would depend on the kind of radiation. She stated that the type often used to treat cancer causes programmed cell death, so normal doses would not trigger alarm signaling. Dr. Matzinger added that protons (sometimes used to treat tumors) do cause cell destruction and alarm signals, whereas x-rays cause programmed cell death. She then recommended that those with autoimmune diseases do what they could to avoid exposures to toxicants and other alarm signal triggers. Mr. Hardie then asked about depleted uranium (DU), with particular concern about inhaled DU and particulate matter from oil well fires. Dr. Matzinger replied that inhalation of DU would not be good, and that she was aware of studies funded by the Gates Foundation looking at oil well fire smoke in an area of Africa where incidence of asthma was very high. She said that she did not know if other symptomatologies had been looked at in this region.

Dr. Sullivan then thanked Dr. Matzinger for her presentation and introduced Mr. Jonathan Gurland, who then conducted the annual ethics training with the Committee.

At the conclusion of the ethics training Chairman Binns called for public comments.

Public Comments

Marie Manteuffel, of the Society for Women's Health Research, submitted a letter to the Committee (see Appendix B – Document 1) and thanked its members for embracing the concept of sex-based differences.

Mr. Bunker then thanked the Committee members for their work.

Mr. Paul Sullivan, executive director of Veterans for Common Sense, thanked the Committee for its 9 years of work. He said that the research and information produced and disseminated by the Committee was giving some hope to veterans and was also letting folks know that science would show what those currently in the room already knew – that Gulf War veterans are sick. He said that veterans were currently just trying to get the word out that they were looking for treatment and a little more recognition from the VA. Mr. Sullivan said that he had the opportunity to look

at the Pre-9/11 report which the Committee had been briefed on earlier, and he said that he would give it a letter grade of about a B. He said there were a few things that could be added, such as the total costs for VA healthcare (not just VISN totals), the total claims for all of VA, and what the whole picture was regarding how many Gulf War veterans the VA was seeing. He said that this question was important because the Veterans Health Administration (VHA) sees some veterans but not all, the Veterans Benefits Administration (VBA) sees some veterans but not all, and the readjustment veteran counseling centers see a third population, and they overlap like three circles in a Venn diagram, and Mr. Sullivan expressed hope that VA would take the data they have, adds it up, and can determine the population of Gulf War veterans that VA is assisting. From there questions can be answered, such as, "Why are we compensating some veterans but not treating them?" and "Why are we treating some veterans but not compensating them?" Mr. Sullivan remarked on the tragedy that many veterans were sick and not getting compensated. Given the lack of time, he said that he would submit a longer written statement for the record (see Appendix B – Document 2).

Dr. Golomb then commented that she had recently seen a self-described Gulf War patient who was 28 years old. She asked if there was separate designation within the VA system for the patients that the Committee knows as Gulf War veterans. Dr. Goldberg remarked that this confusion existed at least partly because Congress had never officially put an end to the Gulf War. He advised anyone seeing a "Gulf War" patient to ask that patient what he or she meant by that term. He said that he tended to use the term "90-91 conflict" and did not include OIF, OEF or any of the current conflicts, but that any presumptive that is made under Gulf War regulations, if it's a presumptive made for 90-91 Gulf War veterans it applies to veterans of OIF and OEF veterans, and vice versa, because those presumptives are made for "Gulf War" the way Congress defined it. Dr. Goldberg added that when the VA submits their reports to Congress the distinction between the different populations is made quite clear.

Mr. Hardie then remarked that not all presumptives applied to Afghanistan veterans (only just the 9 new diseases did). Dr. Goldberg replied that the Secretary of the VA had to use his authority to expand the presumptives to cover Afghanistan, because it is not part of the original Congressional definition of the theater of operations.

Chairman Binns then adjourned the meeting at 5:37pm.

DAY 2

The June 28, 2011 meeting of the Committee was held in Room 1143 of the Lafayette Building at 811 Vermont Avenue, Washington D.C.

Welcome, Introductions & Opening Remarks

Mr. James Binns, Committee Chairman

Chairman James Binns called the meeting to order at 8:50am. He began by thanking everyone for being present and he then welcomed Dr. Timothy O'Leary.

Update of VA Gulf War Cooperative Studies

Dr. Timothy O'Leary, VA Office of Research and Development

Dr. O'Leary began by stating that he would really like to use his time to have a conversation about both studies, first addressing the biorepository (or biobank). He stated that the biorepository was currently under review by the IRB. In addition, he remarked that recruitment strategies were not entirely obvious for the biorepository. He said that it was not necessarily straightforward to write letters to people who were at an age where the rate mortality was relatively low (less than 1 percent). Rather, Dr. O'Leary expressed the desire to somehow advertise the availability of the opportunity to voluntarily join the biorepository. There has been consideration of doing a survey of the Fort Devens cohort to ask them whether they would participate if such a biorepository were made available, and to collect demographic information from the responders. Dr. O'Leary asked for feedback on that idea and recruitment strategies for the biorepository, after remarking that the biobanking techniques being proposed were in conformance with international standards, and that the biorepository was being overseen by Marianna Bledsoe in the VA's Office of Research and Development (ORD).

Dr. Sullivan remarked that, in terms of recruitment, she supported sending letters to the Fort Devens cohort to assess whether that approach might work on a larger scale. She then asked if Dr. O'Leary's concern regarded the long time interval between receipt of the letter and time at which tissue would be ready for donation.

Dr. O'Leary expressed that his greatest concern that sending letters in anticipation of death and donation of tissue to the biorepository might cause distress to the individuals receiving the letters. He added that this might be an issue for the IRB.

Dr. Sullivan replied that her reaction to that concern would be to send letters to as many veterans as possible in order to get as many positive responses as possible.

Dr. Steele remarked that she didn't know whether people would be offended by receiving that letter but that she understood the sensitivity of the issue. She then recommended using the Gulf War Review newsletter to advertise the need for brain tissue for the biorepository, as well as to list other research participation opportunities.

Dr. White remarked that a lot of people contact the Committee to ask how they can participate in studies, and that she would like to see a way to refer those individuals on to the biorepository. Dr. O'Leary said that this would be possible, and that there would be a call center with a call-in number that could serve that purpose. Dr. Sullivan concurred that this would be very helpful. Dr. Steele then recalled one instance in the past when a veteran had contacted the Committee wanting to donate tissue, and she acknowledged the assistance Dr. O'Leary had provided at that time in order to enable that donation to take place. Dr. O'Leary said that the mechanistic techniques had already been worked out for the ALS brain bank.

LTC Knox stated that, as a veteran, she felt people would be more than happy to donate, and that doing so would be no difference from selecting to be an organ donor on one's driver's license. She commented that one great way to get the message out would be include a message on the

veterans' pay or pension stubs. Dr. O'Leary said that he could explore that, but that he had no idea what it would take to get such a message put on those documents.

Chairman Binns then recalled the genesis of the entire project arose from a comment by Paul Greengard about the value of such a biorepository, and that perhaps this could be referenced in the letter that goes out to the veterans. Dr. O'Leary said that he could not promise what would specifically be included in the letter, since ultimately the IRB gets to control all communications, but he said he would certainly explore that.

Dr. Steele then asked what the current plans for recruitment were. Dr. O'Leary replied that the plans included trying to get out advertisements in newsletters already being sent to veterans. He added that plans were in the works for mailings, though getting those out would take a bit of time. That said, Dr. O'Leary said he thought he would be able to piggy-back on a mailing contract called the Million Veteran Program (MVP) which was awarded a few weeks prior. He said that the current question at hand regarded whether to conduct a test mailing with the Fort Devens cohort before rolling out a larger mailing, particularly since the mailings would be expensive and he wanted to be sure that mailings would be an effective way to reach the community.

Dr. White asked if Dr. O'Leary was thinking of the Fort Devens cohort as a pilot for testing the mailing method. Dr. O'Leary replied that this population would be a survey, not a pilot. He added that he had found in developing the MVP that the use of focus groups and survey instruments provided good indications of what the veteran community was likely to respond to.

Dr. O'Leary said that he would also probably use the MVP as an opportunity to advertise opportunities to Gulf War veterans, since 10 percent of the respondents to the MVP thus far self-identified as being veterans of the Gulf War era. He then spoke of the value he saw in combining data on peripheral blood DNA and residual tissue DNA, which he said would be very useful in developing systems biology behind Gulf War Illness and other diseases. Dr. O'Leary said that over time he would like to develop a virtual biorepository bank, identifying individuals who had undergone surgical procedures and who might have tissue samples that could be made available to the research community. He explained that Gulf War veterans could be pulled (as a sub-group) from the MVP along the way.

Dr. Buchwald asked if the Ft. Devens pilot could explore more than just response rate. Dr. O'Leary said that he planned to send a survey that would ask each veteran about a variety of things. Dr. Buchwald then stated that she directs a biorepository of twins from which she collects DNA and has found that there appear to be subtle things that affect response rate. She said that she had assessed response rates according to the mail service used and found that FedEx and USPS First Class mail received similar response rates (both of which were higher than the response rate to regular mail), but that the responses were so similar between FedEx and USPS First Class that it made using USPS (which is much cheaper than FedEx) a real bargain. Dr. Buchwald also remarked that she had found that mailing the newsletter with the request elicited a higher response rate than if only the request was mailed. She added that sending informational materials before the request letter elicited a 75 percent response rate. Dr. O'Leary said that was

useful information and that he would like to talk to Dr. Buchwald further about her recruitment processes.

Dr. Steele then asked if Dr. O'Leary's mentioning of non-brain tissue meant that he was talking about the blood collection biorepository that was also being set up. Dr. O'Leary said that this was not the case, rather he was looking at ways of tapping into existing resources to eventually develop a virtual biorepository for all veterans.

Dr. Sullivan remarked that she had noticed a long list of tissues that were to be collected, according to the protocol she had seen. She asked Dr. O'Leary if this list was still current. Dr. O'Leary said that was still under discussion. He said that one of his concerns was that tissues being collected should be relevant to the research being done so as to avoid collecting a lot of tissue samples that would go unused. What he would like to do is to tailor the types of tissues collected to those which the potential users (scientists) would need. Dr. Sullivan emphasized that brain tissue would be the focus of what the Gulf War research community would be interested in, along with tissues from the liver, spleen and other organs where neurotoxicants could have caused effects.

Dr. Steele then asked if Gulf War veterans were no longer the focus of the biorepository. Dr. O'Leary replied that the virtual biorepository he was describing would be complementary, and not replacing the targeted recruitment of Gulf War veterans for their tissue donations. Dr. Steele then asked if additional tissues would be collected within the Gulf War recruitment protocol. Dr. O'Leary said that he would collect the tissues identified as the most important by the research community. He acknowledged that this science-driven (rather than protocol-driven) approach would allow for a shift over time if research interests regarding Gulf War Illness changed. Dr. Steele then suggested circulating a notice among VA clinicians requesting samples of any biopsies already being taken from any Gulf War veteran patients with unexplained illness that they might be seeing. Dr. O'Leary said he could explore that, though it could be a little tricky to do.

Dr. O'Leary then had to leave for another meeting but said that he would return later in the day to continue the discussion.

LTC Knox then asked if the Committee needed to draft a formal proposal to make suggestions regarding the tissue bank. Dr. Goldberg replied that that would be the most straightforward way to go about it.

Dr. Buchwald remarked that this program was similar in many ways to the federal organ donation program (USRDS). Dr. Goldberg said that early on there was discussion about making the program a passive donation program and there were issues that arose with structuring it that way. Dr. Buchwald said that the reason she brought it up was that she has a project on organ donation and that the motivation behind organ donation varies greatly across individuals, and that understanding why individuals donate would be an important component for strategizing recruitment. Dr. Goldberg replied that he believed this was one of the informational components that would be gathered as part of the Ft. Devens survey. Dr. Buchwald replied that a survey was a quantitative tool, and that she thought qualitative research was needed in order to get at issues

that would be missed by a survey (which she had witnessed in her own work). As an example she stated that there were issues surrounding race and ethnicity that could not be elicited from a survey. Dr. Goldberg said that the conversation could be continued when Dr. O'Leary returned. He then turned the conversation toward Gulf War requests for applications (RFAs).

Dr. Goldberg circulated copies of the three current RFAs and stated that ORD would be adding another pair of RFAs for pilot projects in the areas of general biomedical and clinical trials (though not for new treatments). Dr. Goldberg stated that he was circulating copies of the RFAs to find out if there were any research areas that should no longer be included, or additional topics that should be added. He remarked that he wanted to have the next set of RFAs out on July 8th.

Dr. Steele asked if there was a possibility to include a pilot RFA for new treatments. Dr. Goldberg replied that if the Committee thought that was reasonable a third pilot could be issued. Dr. Steele then asked why pilot studies should not be included in the treatment studies RFA (or in a separate RFA). Dr. Goldberg replied that a lot of the applications received in response to the clinical trial RFA were actually pilots.

Dr. Steele then asked about the timeline for the release of the RFAs. Dr. Goldberg replied that his goal was to have all 6 RFAs posted on the VA intranet and copies sent to all VA research offices by July 8th. He said that the submission window would open on August 15th and close on September 15th.

Chairman Binns asked if the results of the last RFAs had been announced. Dr. Goldberg replied that the results would be announced with enough time for those who did not make it through to revise and resubmit in the next round.

Dr. Sullivan asked if there would be only one round of RFAs this year. Dr. Goldberg apologized for that. Dr. Sullivan expressed concern with this, and requested that an effort be made to return to two rounds of RFAs per year. Dr. Goldberg said that the goal would continue to be twice a year, and stated that this was one reason why a full-time Gulf War staffer was needed in order to ensure that things would run smoothly. Dr. Sullivan asked if progress had been made in hiring someone. Dr. Goldberg replied that the job announcement had been placed, applications had been received, and that things were currently in the hands of HR.

Mr. Hardie then thanked Dr. Goldberg and all at the VA who had worked to draft the RFAs in a way that he felt was reflective of the needs voiced by the Gulf War research community and Gulf War veterans.

Chairman Binns then asked Dr. Goldberg if the discussion could be shifted to another topic until Dr. O'Leary returned. Dr. Goldberg agreed that this would be most productive.

Dr. Meggs then remarked on the comment that Dr. Goldberg had made the previous day regarding the lack of formal recommendations being made by the Committee (outside of the reports that were issued every 4 years). Dr. Meggs stated that the Committee made consensuses at every meeting which were then reported to the Secretary of the VA, and so he asked Dr. Goldberg if communication needed to be improved in order for their recommendations to be

heard. Dr. Goldberg replied that Chairman Binns' letters to the Secretary were, to some extent, considered personal communications rather than formal Federal Advisory Committee recommendations, which he claimed were rarely issued by the Committee.

Chairman Binns then remarked that written recommendations were often issued by the Committee (and could be found on the Committee's website). He said that the Committee could issue more recommendations, but that informal discussion was also necessary (and had been encouraged by Dr. O'Leary at the previous meeting). Dr. Goldberg clarified that he felt informal discussions were often appropriate, but that certain items needed to be formally recommended (for example, the recommendations Mr. Hardie had drafted and circulated regarding the Pre-9/11 report). He emphasized the need for clear Committee decisions to be made, recorded in the transcript and in the minutes, in order to move forward.

Dr. Meggs then proposed concluding each meeting with a list of written recommendations on which the Committee had formally voted. Chairman Binns remarked that he felt the Committee had been doing this, but that the Committee would work on introducing more written recommendations in the future.

Dr. White remarked that in the past the Committee has vetted issues at the meeting, then written formal recommendations after the meeting. She explained that this process was necessary when dealing with complex research strategies or similar issues that require time to think through. Dr. White commented that if the Committee was to be expected to produce formal recommendations at the conclusion of the meetings a separate meeting time of 3-4 hours would be required in order to formalize recommendations. Dr. Goldberg remarked that, as a Federal Advisory Committee, the vote on the final version of the recommendations had to occur as part of a public meeting. He suggested that one solution could be to approve recommendations at the meeting after which those issues and recommendations had been discussed.

Chairman Binns expressed that his understanding was that it was permissible for the Committee to discuss an issue and reach a consensus at a public meeting but then take some time to write and clean up those recommendations at a later point outside the meeting. However, he recognized that some issues (such as the ones being discussed at the current meeting) would probably need to be brought up at a future meeting in order to work out details of the formal recommendation in a public forum. Dr. Goldberg said that as long as the principle issue and decisions were discussed and voted on in public, clean-up of the language outside of the public forum would be acceptable. Chairman Binns then expressed gratitude for Mr. Hardie's ability to draft recommendations overnight, remarking that this was not always possible. Mr. Hardie attested to the fact that doing so was not easy.

Mr. Hardie then asked whether Dr. Goldberg was looking for something more formal than the process by which the Committee had just discussed and agreed upon the recommendation to include an additional RFA for new treatment trial pilots. Chairman Binns said that there was no requirement of Federal Advisory Committees to hold votes, and that agreement via nodding of heads around the table was sufficient.

Chairman Binns then moved the topic toward the Gulf War discussion.

Committee Discussion: VA Gulf War Comprehensive Research Strategy

Mr. Hardie then circulated copies and then reviewed the recommendations he had drafted following the previous day's discussion of the VA Pre-911 report which followed in the place of previous GWVIS reports (See Appendix B – Document 3). He then outlined the recommendations listed in the document, inviting comments and revisions from anyone on the Committee as well as from the audience. Mr. Hardie remarked that the VA should have time to incorporate additional recommendations made at the next Committee meeting in November, since the VA's goal was to complete the Pre-9/11 report by summer 2012.

Chairman Binns thanked Mr. Hardie for putting the recommendations together, stating that he felt the recommendations he had outlined would give the VA a basis for the guidance they would need. He added that he had talked to Mr. Paul Sullivan, the architect of the GWVIS reports, who had stated that he was appreciative of the work that had gone into making the Pre-9/11 report highly informative. Chairman Binns remarked that the essence of Mr. Sullivan's suggestions centered on making the information more usable and specifically focusing still on the Gulf War period as it is commonly known, rather than the definition that Congress had chosen to use. Mr. Hardie then commented that members of the military were trained throughout their service to always look for what was wrong, which did not always mesh with the civilian world where discussing what is right is equally important. He said that he did not want VA to get the impression that he and other veterans were unhappy with the report.

Mr. Meggs then suggested that the Committee hold a formal vote to adopt the recommendations Mr. Hardie had brought to the table at the conclusion of the discussion. Chairman Binns replied that he first wanted the discussion to continue.

Dr. Steele commended Mr. Hardie for his thorough, detailed recommendations, which she said would cause the report to be useful on many more fronts than it currently was if all recommendations were implemented. She then remarked that she had a few tweaks to suggest so that it could be used to determine whether rates of death were higher in one group than another. Dr. Steele remarked that one of the frustrations with the GWVIS reports had been that there was no ability to make such comparisons because the non-deployed veterans were lumped together without regard to age and other necessary characteristics. Dr. Steele recommended defining subgroups of cohorts by the time period of their service.

Dr. Sullivan thanked Mr. Hardie and suggested adding consistency checks of the data because she had noticed that some of the ages of individuals listed as Gulf War veterans were too low to be correct. She said that she suspected these errors may have arisen from miscoded data entries.

Mr. Hardie said that he would like to suggest specific age brackets for the mortality data in the Committee's recommendations. Dr. Steele remarked that she would first like to read the report before advising how to fix it. She also said that she would like to see some clarification in the cohort groups being used.

LTC Knox remarked that the researchers on the Committee would probably want to figure out exactly what was needed amongst themselves. Dr. Steele said that she felt she knew what was needed but did not have the words to convey those details in a way that could be dictated. Mr. Hardie asked if that component could be something that Dr. Steele would bring to the next meeting. Dr. Steele asked if the current discussion had been sufficient enough so that further public discussion of the matter was not necessary.

Chairman Binns stated that since the report would not be issued until the following summer that he would like to circulate Mr. Hardie's comments among the Committee members for further comments, which would set the stage for additional discussion and finalization at the next Committee meeting. He then asked if the Committee was comfortable going forward with Mr. Hardie's drafted recommendations. Mr. Hardie requested that the public be able to make comments.

Dr. Maximilian Buja, Chair of the Gulf War Steering Committee, suggested the need for a searchable database so that individual researchers could pull the cohorts they were interested in. Dr. Steele explained that the report was generated from multiple databases at the VA and DoD, and thus the Committee would need to (and nearly had) agreed on the most useful categories which should be used in the report. Chairman Binns added that having access to those databases would probably be useful, and Dr. Steele concurred. Dr. Steele also remarked that Mr. Salvatore had given the impression that analyses could be run fairly easily using the available databases. Mr. Hardie suggested that the Committee should recommend that the report provide contact information for individuals who might be able to do data runs for researchers making requests for specific data. Chairman Binns and Dr. Sulivan expressed support for this idea, and Mr. Hardie thanked Dr. Buja or his helpful recommendation. The Committee via consensus then agreed that this should be a formal recommendation.

Chairman Binns then called for a brief break. At the conclusion of the break Chairman Binns introduced Dr. Robert Jaeger, the acting Director of Deployment Health.

Dr. Jaeger then introduced Dr. Buja, and acknowledged the other members of the Steering Committee – many of whom were present at the meeting.

Gulf War Research Strategic Plan: 2011-2015

Dr. Maximilian Buja, VA Gulf War Steering Committee

Dr. Buja began his presentation by circulating the meeting minutes and providing an overview of the most recent (April 2011) meeting of the Gulf War Steering Committee (hereinafter referred to as the Steering Committee), which had met three times since its inception (see Appendix B – Document 4).

Prior to Dr. Buja's discussion of the Strategic Plan, Dr. White remarked that the members of the Steering Committee did not review and confer on the Strategic Plan. She therefore expressed confusion over the assertion that the Steering Committee was asked to prepare a two paragraph summary of the Strategic Plan, (see 3rd page of Appendix B – Document 3 or 4). Dr. Buja replied that Dr. White was correct that the steps outlined in the action plan of the meeting minutes had

not been completed yet, and that the Strategic Pan he would be presenting to the Committee was only a draft. Dr. White reiterated that she wanted it made clear that the Steering Committee had not yet vetted the Strategic Plan.

Chairman Binns thanked Dr. Buja for being present at the Committee's meeting and commended him for coordinating efforts between the Committee and the Steering Committee. Dr. Buja said that he would like to continue those efforts, perhaps by scheduling complementary meetings back-to-back. Dr. Hardie expressed appreciation for that effort, particularly for those paying out of pocket.

Dr. Buja then provided an overview of the draft of the VA Gulf War Research Strategic Plan for 2011-2015 (see Appendix A – Presentation 7, Appendix B – Document 5).

At the conclusion of Dr. Buja's presentation Chairman Binns thanked him and Dr. Jaeger for their work and opened the floor to comments from the Committee members, noting that the Committee had only recently received the draft and therefore not had time to prepare detailed feedback.

Dr. Buchwald expressed her support for developing a resource that collects data in multiple domains – both in domains known to be important to Gulf War Illness as well as in exploratory domains that might be but are not yet known to be important. Dr. Buchwald said she supported the creation of cohorts available nationally to all kinds of researchers, and collecting diverse kinds of information that would help the formulation of ideas and hypothesis. She recommended that information be collected on psychological symptoms and stress, particularly because of the connections between immune function and these factors.

LTC Knox said that she had examined the recommendations for case definitions and agreed that biomarkers should be included, but she also wanted to include case definitions that had been used in the past. She asked Dr. Steele which definition she had used in her research, and Dr. Steele replied that she used the Kansas definition, and that some groups used the Fukuda definition. She added that the 2008 Committee report discussed the strengths and weaknesses of 8 documented case definitions. LTC Knox also expressed her desire to look at the effects of synergistic exposures (not just the effects of exposures to individual agents), and the need for an approach that would take into account the connections between the body's psychological and physiological systems.

Dr. Buja commented that the current state of the Strategic Plan was at the level of goal-setting, and that beneath that objectives and strategies for achieving those objectives – such as those being recommended by the Committee – could be plugged in.

Dr. White recommended including timelines and measurable outcomes in addition to goals, objectives and strategies. She said that she felt the Strategic Plan was a good start but that it could be far more visionary, creative about what the introductory statements and goals were. Dr. White felt that timelines were needed for the various aspects of the strategies and general outcomes.

Dr. Buja acknowledged that it was a 5 year plan and ½ of a year had already passed.

Dr. O'Callaghan recommended taking advantage of and building on what has been done in the past. He said that he saw a need for better coordination of the piecemeal efforts going on within the VA, among VA researchers applying for and receiving robust support from the CDMRP, and improved integration of the small cadre of researchers into the greater program with specific goals. Dr. O'Callaghan acknowledged that this issue had been brought up at the last Steering Committee meeting, and that he supported the idea of bringing the researchers together to share failures and successes with one another so as to avoid repeating or duplicating efforts. He acknowledged that this might require a center of excellence and improved cross-talk between investigators with CDMRP funding and those who would be receiving funding from the VA RFAs. Dr. Buja concurred with Dr. O'Callaghan's comments and remarked that the yet-to-be-hired Director of Gulf War Exposure Research would be taking on a lot of these coordination roles.

Dr. Steele said that she concurred with her colleagues in terms of more global principles, but that she was quite disappointed that the draft of the strategic plan was essentially only a statement of goals, and that what was known about Gulf War Illness was not reflected in the document. She said she would like to see that the people putting together the plan understand what has been learned about the illness in question, identify what has and has not been answered as well as the important issues needing to be addressed, and that the plan should put into place a structure and mechanisms needed to conduct the studies which would allow those goals to be met. She said that a lot of the things written in the Strategic Plan about Gulf War Illness did not reflect what was actually known about it (for instance, the claim that exercise showed treatment effectiveness when in fact studies did not demonstrate this). Dr. Steele said that her expertise lay in epidemiology studies and case definition issues, and that the case definition section did not describe what had been learned about case definition, nor describe ways to go about achieving a rational case definition.

Dr. Buja then asked Dr. Steele to confirm that she had concerns about the accuracy of the literature review. She said that was correct. Dr. Buja replied that this section had been written in response to the 21 questions that had been formulated a while ago. He stated that if there were factual errors they would need to be corrected. Dr. Steele remarked that the background/historical piece about the previous planning efforts was accurate, but that the section she had concerns with was the review of the literature on Gulf War Illness. She added that she would be happy to work with whoever was designing that section but that she also had concern about other sections where she did not have expertise. She asked if Dr. O'Callaghan might be able to talk about the section on animal models.

Dr. O'Callaghan remarked that both the biomarker and animal studies objectives were currently so general that they were meaningless in their current form, but that he realized that the document was a draft and would filled in much further moving forward.

Dr. Buja said that he agreed, and reiterated that the report was currently at the level of overall goals, from which point objectives, strategies, timelines and measurable outcomes would be added.

Dr. White then asked whether there were goals around management or an organizational section. She expressed concern that the communication and translation sections were mixed up with research questions. She said that she would have kept those sections separate from research. Dr. White also expressed confusion over how the plan would be managed within VA, and how coordination with CDMRP would play out. She noted that she was currently the chair of the Gulf War Illness Research Program study section at CDMRP. Dr. White said that it would take some tremendous executive thinking to make the Strategic Plan into a cohesive whole, but that it was extremely important to do so. She expressed confidence in the amount of knowledge that VA and had gained about Gulf War Illness in the past 20 years. As such, she felt VA was poised to come up with treatments under appropriate design and management of the Strategic Plan. Dr. White expressed her belief that treatments developed for Gulf War Illness would also have really strong implications for treating other occupational diseases (including pesticide poisoning). She voiced the need for a call to arms about how to produce the best strategic plan, as quickly as possible, with the expertise available.

Dr. Steele concurred that it was time for action.

Mr. Hardie thanked Dr. Buja and the other members of the Steering Committee for being present and for their hard work on the Strategic Plan thus far. He proposed relabeling the 7 existing "strategic objectives" as mechanisms that could help achieve actual objectives, and he then proposed three new topics that he would designate as overarching goals beneath which the "strategic objectives" would fall. These included improving health and lives of Gulf War veterans, better understanding Gulf War Illnesses and a prevention piece that would ensure lessons were learned regarding Gulf War veterans' experiences and exposures. He stated that there might be other broad overarching goals as well, but that those were the three he saw as most important. He felt that the existing 7 "strategic objectives" could easily be reworked so that they fit more appropriately in the Strategic Plan.

Dr. Buja replied that the goals Mr. Hardie outlined were mentioned in the Strategic Plan, but that they could be made more explicit. He then stated that the question which arose was what mechanisms were practically available to help address those goals. Dr. Goldberg replied that he would be able to address some of them when he talked about the cohort.

Mr. Hardie then remarked that the veterans calling in to listen on the phone line were having a difficult time hearing the proceedings. He then made a request for people to speak clearly and slowly into the microphones in order to try to better reach those callers. Chairman Binns then requested that the VA be able to set up and test equipment in advance of the next meeting.

Chairman Binns then asked if the two remaining Committee members who had not yet spoken had anything to say. Dr. Meggs said that he had no comment. Col. Such remarked that in his mind it all came down to proper messaging and organization of the Strategic Plan. He volunteered to spend time assisting with that process if desired.

Dr. Sullivan then recommended more frequent interaction between researchers doing Gulf War Illness research or related, relevant research. She said that if there were ways to utilize existing

networks (e.g. Collexis software) to identify and connect researchers, she believed untapped talent could be recruited from within VA. Dr. Buja replied that Dr. Driscoll had demonstrated the power of that software.

Dr. White then remarked that Dr. Klimas had mentioned holding face-to-face meetings with Gulf War investigators, which Dr. White recalled also having done in the past. She said that those meetings, which lasted several days, often drew many investigators from within and outside the VA. Speaking on a more procedural level, she then commented that the scientific objectives and background had to be verified, relying on the best experts available. Dr. White then asked what plan was needed to get the Strategic Plan into shape.

Dr. O'Leary then said that he was planning a meeting of Gulf War investigators for Spring 2012.

Chairman Binns then reflected back on the Committee's first meeting in April 2002, at which point there was excitement that the Committee had been created and that Secretary Principi (then the Secretary of the VA) had prioritized Gulf War Illness. Chairman Binns said that at that time Secretary Principi had understood the urgency of the issue and encouraged Chairman Binns to have the Committee make interim recommendations as soon as possible, and that the VA would fund them even before a formal report was written up. On his first day Chairman Binns asked the Committee members what the report should say, and they called for a need for biomarkers, treatments, and further research into toxic exposures. Chairman Binns expressed disappointment that the current Strategic Plan did not reach much further than the Committee's initial plan, but he then expressed his optimism regarding two recent advances that could inform the Strategic Plan. The first was VA's large Gulf War cohort study headed by Dr. Han Kang, which showed that an excess of 25 percent of Gulf War veterans had Gulf War Illness. Chairman Binns then noted that the IOM looked at those results and concluded in its most recent report that chronic multisymptom illness was a disease entity. Chairman Binns expressed concern that the VA's current draft of the Strategic Plan quoted the older 2006 IOM report, which did not recognize any unique illness among Gulf War Illness. Chairman Binns said that he would like to see the Strategic Plan updated to reflect these studies, and that doing so was important because the Strategic Plan would become what the field doctors and scientists knew about Gulf War Illness research. He said that he would like to see a renewed sense of urgency in line with that of the recent IOM report, which stated in its vision statement that "the overall goal would be developing effective treatments in order to alleviate [Gulf War veterans'] suffering as rapidly and as completely as possible."

Mr. Hardie said that he would be happy to replace his first proposed overall objective with the statement Chairman Binns had just read. He added that he had recently learned of the opportunity to do tele-health video conferencing between experts and other medical providers in the VA system, which he would like to see included in the Strategic Plan. Mr. Hardie said that over the years many proposals for such a program had been submitted to the CDMRP, and he felt it could be utilized to benefit the Gulf War veteran population and to maximize the existing resources of the VA (namely experts in different diseases relevant to Gulf War Illness). Mr. Hardie then asked for the Committee's input regarding if, how or where this recommendation could be worked into the Strategic Plan.

Dr. White remarked that the Strategic Plan currently included an element focused on the translation from bench to bedside, which she felt would encompass tele-health initiatives and other strategies. She agreed that this was a visionary approach that should be included in the Strategic Plan.

Dr. Goldberg remarked that he wanted to be careful to distinguish between dissemination of research findings into new treatments vs. recommendations on how VA delivers clinical care. He explained that the latter was a topic that would be dealt with by the VA Task Force, rather than the Committee. He agreed with Mr. Hardie that the issue was an important one, but expressed uncertainty about the research Committee's role in addressing clinical issues.

Chairman Binns then suggested that experts from the Committee, the Steering Committee and some of the VA staff and researchers together develop very specific recommendations to the VA regarding the Strategic Plan. He acknowledged that it would take a lot of work and some time, but that he hoped by the next meeting something could be presented to the VA in a public forum.

Dr. Buja then remarked that it was his understanding that the Strategic Plan was in the hands of the Steering Committee, and that work would need to proceed electronically. He said he envisioned assigning sub-committees comprised of members of the Steering Committee and the Committee to work on developing the Strategic Plan, at least to the level of specific objectives for each of the major goals. Dr. Buja said he hoped the document could then be circulated electronically and discussed at a joint session of both committees in November.

Dr. White expressed concern that November was too far off in the future. Dr. Buja replied the best solution would involve everyone canceling their plane reservations and staying at the meeting until a plan was worked out. Dr. White replied that if sub-committees were going to be created she felt that the Steering Committee would need to discuss and identify the sub-sections. She added that a September 1, 2011 deadline for each sub-committee would be appropriate in order to have something significant to bring to the table come November. Dr. Buja agreed, noting that there would need to be a lot of discussion and negotiation in order to reach a consensus.

Dr. Joel Kupersmith, Chief Research and Development Officer at VHA, stated that there would be no stopping to wait for the strategic plan. He gave an example the recruitment that was ongoing as part of the MVP. Dr. Kupersmith acknowledged that although strategic plans could take time to write and finalize in words, much of what was written in them could be accomplished simultaneously, which he hoped would be the case for this Strategic Plan. He also expressed his appreciation for the acknowledgement that the Committee had made regarding the VA's progress. He said that it was up to Dr. Buja to decide how the development of the Strategic Plan should go.

Dr. Buja then remarked that the high-level objectives outlined by Mr. Hardie could go in a preamble. He said that he was comfortable with the components he suggested, but that he felt a National Resource Repository should also be included in order to specifically address the need for a cohort. Dr. Buja said that he would then like to assign Dr. White to work on the case

statement, Dr. Tilo Grosser to work on the genomics, and others to address the additional objectives prior to the next Committee meeting in November.

Dr. Kupersmith then spoke about an element of the Strategic Plan which had not been discussed yet, which was the aim to use available VA resources to develop parts of the Strategic Plan. As an example, he mentioned that he would like to see the Evidence-based Synthesis Program (ESP) used. He stated that this type of efficient use of resources would be necessary in the context of government budgetary constraints.

Chairman Binns stated that he would like to see the planning move forward with good collaboration between the Committee and the Steering Committee. He remarked that he also saw potential for changes in the direction of the Strategic Plan which could modify what the VA was on course to do, and that the Strategic Plan should be what drives the activity.

Dr. Kupersmith said that he understood, but that he wanted to assure the Committee that he had not stopped working on the issues at hand. He gave the example of the development of the genomics database as a piece of the program that was under development.

Dr. Buja commented that he wanted to select 2 or 3 people with expertise to lead each of the sub-committees, including VA staff.

Dr. White asked Dr. Buja if a group could be created to deal with the management aspects of the Strategic Plan. She felt that the VA needed to be a part of it but that that a management plan was also needed. Dr. Buja replied that this would probably fall under the purview of the yet-to-be-hired Director of Gulf War Research.

Chairman Binns remarked that he was reminded of the Committee's efforts to get the University of Southwestern (UTSW) Gulf War research group to identify how they were going to manage their research program and that had never been a strength of their plan. He said he would like to see the management plan for VA's Strategic Plan strengthened as well.

Dr. Steele then reiterated that she saw the need for a management structure as well, particularly given the IOM's call for a Manhattan-style project.

Dr. Buja said that he was going to propose adding 2 additional elements. He said one objective would focus on the cohorts of people on which all of the studies would be based, including accurate case definitions. The other element he would like to add would be a management plan.

Dr. Meggs then remarked that one thing that had inhibited work in the field and care for the Gulf War veterans was the lack of a knowledgeable and interested clinician at each major VA health center who could act as a point person for Gulf War health issues. He expressed doubt that every VA clinician would be able to be trained, and that designating a point person could be a productive and effective solution.

Dr. Kupersmith said there had been some discussion of that type of solution, and that the closes field of expertise appeared to be occupational medicine, which was not a highly populated field within the VA.

Dr. Jaeger then thanked everyone for their constructive comments.

Dr. Klimas then commented that, as one of the individuals who bridged research and clinical care within the VA, she saw great promise in a train the trainer program (modeled after the HIV/AIDS program instituted at the VA). Dr. Kupersmith agreed that this was a good suggestion.

Dr. Steele then asked if any of the existing RFAs would accommodate funding for a VA researcher to develop a train the trainer program, which would involve research into the best way to implement such a program. Dr. Kupersmith replied that it could be explored.

Mr. Hardie said that if it were possible to do that he felt it would address one of the concerns he had raised earlier. He added that he had seen applications submitted to the CDMRP which proposed to look at whether treatment delivery systems were effective. Dr. Kupersmith said that the VA was in very early stages of discussion, and that there was a long way to go. Mr. Hardie asked Dr. Kupersmith the please communicate to others at the VA that however it could be achieved would be appreciated.

Chairman Binns then thanked Dr. Buja and everyone on the Steering Committee for their time and interest before transitioning the conversation back the morning's discussion with Dr. O'Leary.

Committee Discussion: VA Gulf War Comprehensive Research Strategy (continued)

Dr. O'Leary then remarked that he did not like the analogy made to the Manhattan project, which involved engineering and physics which was known before the development of the atom bomb, as opposed to Gulf War Illness, for which there was not a known systems biology understanding of disease. He stated that the task at hand for the Gulf War research program was thus to explore the plausible causalities through various routes of inquiry, including the genetics and cohort studies.

Dr. Steele remarked that a systems biology approach was not needed before progress could be made. Dr. O'Leary agreed, but emphasized that he was just trying to draw a distinction between the two projects. Dr. Steele remarked that it had been the IOM's analogy, not hers, and Dr. O'Leary acknowledged that.

Dr. O'Leary then described the MVP, which he described was an attempt over a 5-7 year period to create a biorepository which would be linked to information from the VA electronic health record. He said that of the 6,000 survey respondents who expressed interest in participating, just over 10 percent indicated as part of their questionnaire response that they had served during the Gulf War era time period. Chairman Binns then asked for clarification of exactly what time period Dr. O'Leary was referring to. He said that this was the self-identified 1991 time period,

but that this was not the only source of data on service period. Dr. O'Leary said that it would be possible to link to further information through the DoD's deployment health database. Dr. O'Leary stated that the MVP also involved a short form and voluntary long form that served as an epidemiological survey document covering a variety of health conditions. Dr. O'Leary then outlined options for the future development of the Gulf War veteran cohort. He said that one of the most straightforward ways would be to pull individuals from the growing MVP database. He explained that the machinery was already in place and that the MVP would be at 27 medical centers within the current fiscal year, and would be in 40-50 centers by sometime in 2012. Dr. O'Leary stated that once the MVP reached 50 centers it would have achieved reasonable geographic coverage to reach 80 percent of veterans in the United States who use the VA medical system.

Dr. Steele asked if the MVP was only used to recruit veterans from VA medical centers. Dr. O'Leary replied that this was correct. He said that he recognized that this was not a complete subset of veterans who served in any area but that it was an in-depth subset of veterans. Dr. O'Leary remarked that most VA research studies involved only (or primarily) veterans who utilized the VA medical system. He said that a study had found that the likelihood of veterans participating in the MVP was driven by their degree of satisfaction with their healthcare experiences. Dr. O'Leary stated that about 20 percent of veterans were agreeing to participate in the MVP early on, and he was optimistic that the enrollment rate would increase as the program expanded. He remarked that the recruitment was driven centrally, but that the MVP visit involving the consent form and blood collection could be coordinated with a veteran's routine healthcare visit. Dr. O'Leary added that informatics resources were also being built up as part of the MVP so that investigators could do data analyses (on de-identified datasets). He said that within the first year of operation he hoped to see 50,000-100,000 individuals recruited. He said that the recruitment rate was largely driven by the time required by the contractor to gear up on mailing, scanning and expand the telephone call center.

Dr. Steele then asked if a contractor was already in place. Dr. O'Leary replied that the contract had been let but that he did not remember who the specific contractor was. He said that the contractor was supposed to be fully operational within 3 months, but that this timeline might be overly optimistic.

Dr. O'Leary then described an alternative option to simply building upon the MVP database. The other option he presented was to start with the DoD dataset and to try to recruit individuals using blind mailings as well as to contact individuals from cohorts studied previously. He recalled that the discussion about this recruitment option that took place at the previous Committee meeting brought up a concern with the survey information to be gained. Dr. O'Leary then posed a design question to the Committee. He stated that a lot of survey data existed already (through registry surveys and from Dr. Han Kang's research), and that he did not want to replicate all of this existing data if it was not necessary – particularly as he was concerned with survey fatigue. Dr. O'Leary said that he had done a side-by-side analysis of the various studies that had been done and there was no individual study that had addressed every issue which had been raised by the Gulf War community, but that he felt the VA registry study had maximized at least coverage of the various issues associated with Gulf War veterans' health issues. Dr. O'Leary said that he did not think every question asked in the original registry survey would need to be asked again in the

current survey, since some were no longer relevant. He then asked for the Committee's comments on the direction that the survey should take, with particular regard to what if any added scientific value they would expect from reaching out to veterans who were not receiving VA healthcare. He also asked the Committee which exposures they thought would be the most important to include in the epidemiologic survey.

Dr. Steele remarked that she had extensive experience designing survey instruments and that treatment-seeking populations differ from the population not seeking treatment, and that this holds true for Gulf War veterans. She explained that many Gulf War veterans with multisymptom illnesses had given up on the VA healthcare system. Dr. Steele said that some questions could be answered within a clinical population (i.e. a cohort consisting only of veterans who had sought care in the VA healthcare system) but other questions such as those pertaining to prevalence of disease could only be answered by using a population-based sample (i.e. by including veterans outside of the VA healthcare system).

Dr. O'Leary stated that he thought that he would create a separate design group to address this issue with regard to the MVP, because the population was still being recruited. He then provided an overview of the status of the genetics component, and remarked that the decision on the analytical methodology for the genetics study would fluctuate over time as genetics research continues to advance and procedural costs continue to drop. Dr. O'Leary explained that the CSP 585 was set up as a pilot study aimed at looking at the recruitment question. He said that it had been put on hold after the past Committee meeting raised some questions which Dr. O'Leary had wanted look into. He explained that the pilot study was going to involve a survey mailing to 10,000 veterans, using the same machinery as was being used for the MVP. He then discussed the options that were on the table for the blood sample collection component of the study. Dr. O'Leary said that he had considered contracting outside labs but that it was expensive and complicated. He said that saliva collection was being considered, but that sample would not include biomarkers that would be found in serum.

Dr. Sullivan then remarked that one benefit of collecting saliva was that it could be mailed in, which made data collection easy. Dr. O'Leary agreed, but stated that he was not sure that saliva would be adequate for studying the full genome if the study moved in that direction. He said that if adequate blood specimens could not be collected that he would consider using saliva. He further explained that ultimately the data gathered from this pilot would be linked to the tissue bank. Dr. O'Leary remarked that the pilot was currently undergoing IRB review and that he did not foresee any issues arising if the survey instrument changed as a result of the Committee's discussion that day.

Dr. Steele then asked if the survey included in the version that the IRB was reviewing was the VA National Survey questionnaire. Dr. O'Leary said that he believed it was, but that would not be a major issue to the IRB.

Dr. Steele said that she thought it would be hard to identify questions that would be informative for Gulf War veterans that would get at the important issues (even from the MVP) but that would not overburden the --- at this point Dr. O'Leary interjected with the remark that the MVP short form questionnaire was currently being used to generate baseline information for all blood

collection studies. He acknowledged that it was not a perfect instrument but that it was enough to help develop target studies in the future, which was the underlying design philosophy. Dr. O'Leary said that the questionnaire as a whole had not been independently validated but that all of its components had been.

Dr. Sullivan then asked if the CSP 585 questionnaire was still being used for the brain biorepository, and suggested if not that some other health symptom survey be circulated to determine whether donors had Gulf War Illness or not. She suggested that Dr. Steele's short questionnaire could be used.

Dr. Marianna Bledsoe, who was recruited from the NIH tissue banking policies and programs to oversee the biorepository and other VA efforts, responded to Dr. Sullivan's question. She acknowledged that it was not stated in the protocol, but that the current plan for the brain biobank was to use the MVP baseline survey, the structured neurotoxicant assessment checklist (SNAC) for exposure data and to also collect some data on symptoms. Dr. Sullivan expressed her support for the inclusion of those questions.

Dr. Meggs then remarked that exposures followed location in theater and location in theater followed units. As such he wondered if data on unit locations in the Gulf War theater would be incorporated into the database. Dr. O'Leary said that he was hoping to link to that information through the DoD dataset.

Dr. Steele then asked Dr. Bledsoe to clarify what symptoms were identified using the SNAC. Dr. Bledsoe said that this included symptom questions used to identify Gulf War Illness by the Kansas definition and chronic multisymptom illness by Fukuda case definition. Dr. Steele and Dr. Sullivan thanked Dr. Bledsoe for that information.

Mr. Binns then asked if the Committee thought it would be adequate to use only the Gulf War veterans identified only by the MVP. Dr. O'Leary said that based on Dr. Steele's comments he felt that it would be necessary to include additional veterans outside of the MVP, which he said was what had been originally planned. Dr. Steele replied that a pilot of 10,000 might reveal the differences, which might or might not be of a nature that would affect the ability to answer important questions using only the MVP population.

Dr. Steele then asked if the 10,000 veterans selected to receive mailed surveys for the study would be drawn from the longitudinal follow-up cohort established by Dr. Han Kang (which she recommended). Dr. O'Leary stated that the original plan was to select recipients from the VA DoD identity repository but that he could look at that question, and he agreed that there was an advantage to using that cohort since additional data on those individuals already existed.

Chairman Binns then asked if the survey instruments covered all of the questions that needed to be covered, which he remarked had been an issue from the UTSW study, and he also asked if the issues with the latest draft of the VA's large survey had been resolved based on the day's discussion. Dr. O'Leary said that the issues had not been resolved but that he thought he had an approach for resolving it. He said that in this case he wanted to have the study team contact individuals with expertise to serve as consultants.

Chairman Binns then asked what the estimated cost of the first year for CSP 585. Dr. O'Leary said that he wasn't positive because it depended on exactly when the program launched, but that numbers should be listed in the materials circulated. Dr. Steele referred to the budget allocations document (see Appendix B – Document 6), and remarked that the amount for fiscal year 2010 was $28,000. Dr. O'Leary said that Dr. Steele was not reading the correct number. He said he could not remember the exact budget line but that he estimated it would cost about $100 per enrollee (based on the typical enrollment cost for a VA study). He said that the budget for CSP projects was actively managed over time and was driven by the ultimate goal, such that if the project required going over budget to meet the goals of the study that could be done, even if that meant a 10-15 percent increase in cost over the original budget estimate.

Chairman Binns then remarked that he would be asking the Committee staff to review the budget items to ensure that they were all highly relevant to Gulf War Illness. Dr. O'Leary said that he should be able to get a more precise number to the Committee. Chairman Binns then thanked Dr. O'Leary and, with reference to materials distributed at the last minute during the previous meeting, requested that in the future documents be provided in advance of the meeting so that the Committee members could read, reflect and ask important questions during the meeting. Chairman Binns then stated that he would like the Committee to issue a formal recommendation with regard to the Strategic Plan, and that the elements should include appreciation for the creation of the drafted plan, a statement that the Committee felt the characterization of past history was inaccurate with respect to what Gulf War Illness shows, and with respect to the future that the report hit the top goals but needed to be fleshed out with objectives, strategies, timelines and measurable outcomes. He suggested the inclusion of a statement that the Committee would be participating in the process of helping develop more detailed recommendations to be considered at the next Committee meeting. Committee members indicated their agreement with this recommendation.

Dr. Kupersmith then remarked that he had been working at his current job for 6 years and that many recommendations had been exchanged between this Committee and other groups, and that the Strategic Plan gave everyone a structure and specific around which to build discussion. He said that it would be a synthesis of everyone's contributions and as such was an indication of progress.

Chairman Binns then thanked the members of the VA for their interest in creating a dialogue, then he adjourned the meeting.

THIS PAGE INTENTIONALLY LEFT BLANK