Research Advisory Committee on Gulf War Veterans' Illnesses

November 1-2, 2010, Committee Meeting Minutes

Boston University School of Public Health
Boston, MA

Research Advisory Committee on Gulf War Veterans' Illnesses
Boston University School of Public Health
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I hereby certify the following minutes as being an accurate record of what transpired at the November 1-2, 2010 meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses.

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

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Attendance Record

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

Committee Staff
Kimberly Sullivan
Sadie Richards

Designated Federal Officer
Bill Goldberg

Guest Speakers
Dane Cook
Jeffrey Mogil
Kenneth Jeffrey Myers
Richard Clapp
Carl Hauser
Lea Beaulieu
Jean van Seventer
Christopher (Kit) Brady
Neil Kowall
Steven Perrin
Lisa Conboy
Ann Louise Oaklander
Max Klein

* participated by phone

Abbreviations

AChE – Acetylcholinesterase

ALS – Amyotrophic Lateral Sclerosis

ALS TDI – Amyotrophic Lateral Sclerosis Therapy Development Institute

BBB – Blood-Brain Barrier

BUSPH – Boston University School of Public Health

CDC – Center for Disease Control

CDMRP – Congressionally Directed Medical Research Programs

CFS – Chronic Fatigue Syndrome

CMP – Chronic Musculoskeletal Pain

CNS – Central Nervous System

CT – Computed Tomography

CTE – Chronic Traumatic Encephalopathy

CV – Conduction Velocity

DAMPs – Damage-Associated Molecular Patterns

DoD – Department of Defense

DU – Depleted Uranium

EES – Environmental epidemiology Service

EIH – Exercise-Induced Hypoalgesia

EMG – Electromyogram

ENF – Epidermal Nerve Factor

ERIC – Epidemiologic Research and Information Center

FDA – Food and Drug Administration

fMRI – functional Magnetic Resonance Imaging

GERD – Gastroesophageal Reflux Disease

GFAP – Glial Fibrillary Acidic Protein

GWA – Genome-Wide Association

GWI – Gulf War Illness

HIV – Human Immunodeficiency Virus

IBS – Irritable Bowel Syndrome

IP - Intraperitoneal

IOM – Institute of Medicine

IRB – Institutional Review Board

JCAHO – Joint Commission on Accreditation of Healthcare Organizations

MAPP – Multidisciplinary Approach to the Study of Chronic Pelvic Pain

MS – Multiple Sclerosis

NIDDK – National Institute of Diabetes and Digestive and Kidney Diseases

NIH – National Institutes of Health

OP – Organophosphorous

OPIDN – Organophosphate-Induced Delayed Neuropathy

ORD – Office of Research and Development

PAMPs – Pathogen-Associated Molecular Patterns

PB – Pyridostigmine Bromide

PCBs – Polycholorinated Biphenyls

PCR – Polymerase Chain Reaction

PET – Positron Emission Tomography

PCBs – Polychlorinated Biphenyls

PD – Pre-clinical Development

PTSD – Post-Traumatic Stress Disorder

RA – Rheumatoid Arthritis

RFA – Request For Applications

ROS – Reactive Oxygen Species

SFPN – Small-Fiber Polyneuropathy

SIR – Systemic Inflammatory Response

SOD – Superoxide Dismutase

TBI – Traumatic Brain Injury

TCM – Traditional Chinese Medicine

TLR – Toll-Like Receptor

UCSD – University of California at San Diego

VAB – Veterans Affairs Biorepository

VACO – Veterans Affairs Central Offices

VHA – Veterans Health Administration

WRIISC – War-Related Injury and Illness Center

Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses
November 1-2, 2010

Boston University School of Public Health, 670 Albany Street, Room 107, Boston, MA

Agenda
Monday, November 1, 2010

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	**Innate immunity, inflammation and Toll-like receptors**	**Dr. Jean van Seventer** **Boston University School of Public Health**
9:30 – 10:15	**Mitochondrial Damage Associated Molecular Patterns (DAMPS) and inflammation**	**Dr. Carl Hauser** **Beth Israel Deaconess Medical Center** **Harvard Medical School**
10:15 – 10:30	**Break**	
10:30 – 11:15	**Toll-like receptors, thrombosis and the relationship to Gulf War Illness**	**Dr. Lea Beaulieu** **Boston University School of Medicine**
11:15 -12:00	**Chronic inflammation in ALS and potential therapeutic strategies**	**Dr. Steven Perrin** **ALS Therapy Development Institute**
12:00 – 12:30	**Committee Discussion with previous presenters**	**Res Adv Cmte Gulf War Illnesses**
12:30 – 1:30	**Lunch**	
1:30 – 2:15	**Gulf War Brain Bank update**	**Dr. Neil Kowall** **Dr. Christopher (Kit) Brady** **VA Boston Healthcare System**
2:15 – 3:00	**Small-fiber polyneuropathy: A potential Contributor to GW illness**	**Dr. Anne Louise Oaklander** **Dr. Max Klein** **Massachusetts General Hospital**
3:00 – 3:15	**Break**	
3:15 - 4:00	**The Nature and Nurture of Pain**	**Dr. Jeffrey Mogil** **McGill University**
4:00 – 4:45	**Exercise and pain studies in GW Illness**	**Dr. Dane Cook** **William S. Middleton Mem Veterans Hospital**

4:45 – 5:15 Public comment

Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses
November 2, 2010

Boston University School of Public Health, 670 Albany Street, Boston, MA

Agenda
Tuesday, November 2, 2010

8:00 – 8:30	**Informal gathering, coffee**	
8:30 – 9:00	**Toxicogenomics overview**	**Dr. K. Jeffrey Myers** **Malcom Randall VA Medical Center**
9:00 – 10:00	**Epidemiology of brain and other cancers**	**Dr. Richard Clapp** **Boston University School of Public Health**
10:00 –10:45	**The effectiveness of acupuncture in the Treatment of Gulf War Illness**	**Dr. Lisa Conboy** **The New England School of Acupuncture**
10:45 – 11:00	**Break**	
11:00 –11:30	**Update of VA Gulf War research**	**Dr. William Goldberg** **VA Office of Research and Development**
11:15 – 11:30	**Break**	
11:30 – 12:30	**Committee discussion: 2011 Planning**	**Mr. Jim Binns, Chairman** **Dr. Kimberly Sullivan** **Res. Advisory Cmte Gulf War Illnesses**
12:30 – 1:00	**Public Comment**	
1:00pm	**Adjourn**	

DAY 1

The November 1-2, 2010 meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses (hereinafter referred to as the Committee) was held at Boston University School of Public Health, at 670 Albany Street, Room 107, Boston, MA 02118.

Welcome, Introductions & Opening Remarks

Mr. James Binns, Committee Chairman
Dr. Roberta White, Committee Scientific Director
Dr. Kimberly Sullivan, Committee Scientific Coordinator

Chairman James Binns called the meeting to order at 8:30am. Dr. Roberta White then welcomed everyone. Dr. Kimberly Sullivan then reminded the Committee of the discussion planned for the following day before providing a framework of the morning's talks (see Appendix A – Presentation 1). She began by explaining that Gulf War Illness (GWI) is a complex illness that is not only a multisymptom disorder but also a multi-system disorder that generally includes fatigue, joint and muscle pain, cognitive difficulties, gastrointestinal distress, breathing problems and skin rashes that vary among individuals. Dr. Sullivan then stated that recent research suggests that there may be a mechanism for GWI that encompasses the cross-talk pathways among the different systems shown to be affected in Gulf War veterans including the Central Nervous System (CNS), immune system and the coagulation system. She explained that several experts in their respective fields would therefore be discussing how these cross-talk pathways might interact to cause chronic inflammation and innate immune effects in different diseases. After her overview, Dr. Sullivan introduced the first speaker, Dr. Jean van Seventer.

Innate Immunity, Inflammation and Toll-Like Receptors

Dr. Jean van Seventer, Boston University School of Public Health (BUSPH)

Dr. van Seventer provided an overview of inflammation and the immune response (see Appendix A – Presentation 2). Her presentation included discussion of the positive and negative outcomes of the immune response, toll-like receptor (TLR) biology and innate immunity in the CNS. Dr. van Seventer explained that the body has an innate and an adaptive immune response, and that white blood cells mediate both. She explained that cells of the innate immune system utilize toll-like receptors to recognize microbes via motifs known as pathogen-associated molecular patterns (PAMPs). Dr. van Seventer also briefly discussed microglia, the immune cells of the CNS, which express variable levels of toll-like receptors and are implicated in chronic demyelinating diseases through cycles of activation, release of pro-inflammatory cytokines and tissue destruction.

Dr. Sullivan thanked Dr. van Seventer for her presentation and then asked the Committee if they had any questions.

Dr. Bill Meggs, a member of the Committee, asked if exposure to organophosphorous (OP) compounds could dysregulate the innate immune system of the CNS. Dr. van Seventer replied that if the OP compounds have an effect that would initiate inflammation in the CNS that could result in local tissue destruction and the release of mediators by activated microglia.

Dr. Sullivan asked Dr. van Seventer to talk about the activation of the adaptive immune system by the innate immune system in the context of chemical exposures. Dr. van Seventer replied that theories exist about autoimmune diseases arising from exposure to chemicals which trigger changes in endogenous molecules so that they look like exogenous compounds and are thereby susceptible to attack by the immune system.

Dr. Sullivan then introduced the next speaker, Dr. Carl Hauser.

Mitochondrial Damage Associated Molecular Patterns (DAMPS) and Inflammation

Dr. Carl Hauser, Beth Israel Deaconess Medical Center, Harvard Medical School

Dr. Hauser began his presentation by briefly describing the systemic inflammatory response (SIR) before discussing the role of mitochondria in inflammation (see Appendix A – Presentation 3). He then described his research on mitochondrial DNA, including his finding that mitochondrial DNA activates a specific toll-like receptor (TLR9) that typically recognizes bacteria. Dr. Hauser's research has also found that injuries cause the release of mitochondrial DNA into the bloodstream. Taken together, Dr. Hauser explained that these findings suggest that levels of mitochondrial DNA found in the bloodstream after tissue injury are capable of triggering inflammatory signaling cascades.

At the conclusion of Dr. Hauser's presentation, Dr. Lea Steele, a member of the Committee, asked what fluids were measured for mitochondrial DNA. Dr. Hauser replied that plasma or whole blood could be used. Dr. Steele then asked if Dr. Hauser would expect to find elevated levels of mitochondrial DNA in individuals experiencing lower level inflammation. Dr. Hauser replied that he did not know. Dr. Steele asked if comparable findings might be made in the brain. Dr. Hauser responded that he was currently working with Dr. Mervin Maze to research the potential activation of glia by systemic inflammation. Dr. Steele asked how the cholinergic control of inflammation might interface with his mitochondrial findings. Dr. Hauser replied that he did not know, and that much more research needed to be done.

Dr. Beatrice Golomb, a member of the Committee, then expressed her uncertainty regarding how Dr. Hauser's findings might tie in to Gulf War veterans. She asked if conditions of ongoing oxidative stress might be capable of triggering apoptosis and cause the release of mitochondrial DNA as a result. Dr. Hauser replied that he would not expect apoptosis to release mitochondrial motifs, but that apoptosis might be a downstream event resulting from exposure to mitochondrial DAMPs. Dr. Golomb then remarked that apoptosis was known to trigger inflammation and coagulation pathways. Dr. Hauser replied that more research needed to be done, and that his assertions were a working hypothesis.

Dr. Jim O'Callaghan, a member of the Committee, then asked if there was any evidence for altered blood-brain barrier (BBB) due to release of mitochondrial DNA. Dr. Hauser stated that he was planning to conduct an experiment in mice that would involve looking at brain cells following exposure to mitochondrial DNA. Dr. O'Callaghan remarked that the prevailing view is that the BBB remains intact in the presence of massive endotoxin. Dr. Hauser accepted Dr. O'Callaghan's assertion.

Dr. Dedra Buchwald, a member of the Committee, commented that she was involved in a study of response to acute lung injury in 300 twins, and then asked what was known about the genetic or environmental influences on these types of responses. Dr. Hauser replied that there was a growing body of knowledge regarding polymorphisms of inflammatory receptors and downstream transcription factors that may be activated in different ways across individuals exposed to the same concentration of mitochondrial DNA, and that more research was needed. Dr. Buchwald followed up by asking if there were differences in outcomes by race or ethnicity. Dr. Hauser replied that there were not any findings that he knew of, though he knew of several ethnicities that respond less well to certain things. He added that the studies he had been speaking of were process studies, not outcome studies.

Dr. Sullivan asked what test Dr. Hauser would recommend in order to investigate whether mitochondrial DNA was detectable in the blood of Gulf War veterans experiencing lower level inflammation. Dr. Hauser replied that the polymerase chains reactions (PCRs) he uses were very sensitive, but that detecting small amounts of mitochondrial DNA (near the limit of detection) might not indicate abnormality. He added that he was currently in the process of developing mass spectroscopy-based tests for peptides (other mitochondrial products). Dr. Hauser then mentioned that mitochondrial lipids might also be immunoactive. Dr. Sullivan asked if there were tests available for that and Dr. Hauser replied that Polly Matzinger would know.

Dr. Neil Kowall of the Boston VA asked what the time course was for mitochondrial DNA in the blood. Dr. Hauser replied that the only study he had done was in shock, where peak levels of mitochondrial DNA occurred 3 hours after exposure. He stated that prolonged release of mitochondrial DNA might have different effects. Dr. Hauser then remarked that he believed any disease process which leads to cellular damage could potentially lead to release of mitochondrial motifs.

Dr. Sullivan remarked that the question of genetic polymorphisms then became whether that would make others more vulnerable to continued illness. Dr. Hauser replied that he did not think anyone had looked at polymorphisms of receptors such as TLR9, though existing libraries might contain the data necessary to find out.

Dr. Sullivan then thanked Dr. Hauser for his presentation and Mr. Jim Binns called for a 15 minute break. After the break, Dr. Sullivan introduced the next speaker, Dr. Lea Beaulieu.

Toll-Like Receptors, Thrombosis and the Relationship to Gulf War Illness

Dr. Lea Beaulieu, Boston University School of Medicine

Dr. Beaulieu began her presentation by providing an overview of Gulf War Illness and how toll-like receptors might be implicated in producing the characteristic symptoms of GWI before discussing her research of the roles of toll-like receptors, specifically TLR2, in bone marrow cells known as megakaryocytes which produce platelets (see Appendix A – Presentation 4). One of Dr. Beaulieu's conclusions was that through TLR2, inflammation can regulate thrombosis and could be a link between the coagulopathy and inflammation in Gulf War Illness.

At the conclusion of Dr. Beaulieu's presentation, Dr. Golomb recalled that increases in fibrinogen and thrombin had been observed in ill Gulf War veterans, and asked if there had been any findings related to platelets in ill Gulf War veterans. Dr. Steele commented that increased tissue factor production by platelets had been observed, but that those findings had not necessarily held up, according to Dr. Ron Bach. Dr. Golomb then commented on the important role of microtubules, noting that organophosphates damage microtubules. She then expressed interest in seeing studies that compared subsets of Gulf War veterans who had been exposed to organophosphates vs. those who had not.

Dr. Sullivan then commented on Dr. Beaulieu's research on TLRs in the cardiovascular system, and asked Dr. Beaulieu whether she might expect TLR antagonists to be helpful in treating inflammatory conditions and hypercoagulation such as that seen in Gulf War veterans. Dr. Beaulieu replied affirmatively, noting that the original application of TLR antagonists (namely two TLR4 antagonists) was to treat sepsis and shock, but that they also had been found to help recovery in mouse models of myocardial ischemia and repurfusion. She added that, to her knowledge, TLR2 antagonists had not yet been investigated, and that system-wide antagonism of TLRs would not be beneficial to health. Dr. Sullivan followed up by asking if these TLR4 antagonists were known to cross the BBB. Dr. Beaulieu did not know if they could.

Dr. Hauser then asked if there were any known endogenous agonists for TLR2. Dr. Beaulieu replied that saturated fat and certain lipoproteins could activate TLR2. Dr. Golomb followed up on Dr. Hauser's question by asking if Dr. Beaulieu knew what saturated fat had been studied. Dr. Beaulieu replied that the study she knew of had used palmitate, and that omega-3 fatty acids had also been found to bind to TLR2, but with opposing effects.

Dr. Sullivan then thanked Dr. Beaulieu before introducing the next speaker, Dr. Steven Perrin.

Chronic Inflammation in ALS and Potential Therapeutic Strategies

Dr. Steven Perrin, ALS Therapy Development Institute

Dr. Perrin provided a brief overview of Amyotrophic Lateral Sclerosis (ALS), then discussed his organization's research approaches and findings regarding ALS and disease treatment using mouse models and human tissue studies (see Appendix A – Presentation 5). In his presentation, Dr. Perrin pointed out the importance of controlling for gender differences in the ALS animal model. Dr. Perrin also discussed his drug screening findings of a blocking antibody (anti CD40L) to one of the two arms of the co-stimulatory pathway which has been well investigated in other pre-clinical models of autoimmune diseases and tissue transplant. Blocking CD40L signaling with this antibody delayed disease onset, slowed its progression, and improved survival in the ALS mouse model. One of Dr. Perrin's overarching take-home messages was that comprehensive and unbiased molecular profiling can identify molecular pathways amenable to therapeutic intervention.

At the completion of Dr. Perrin's presentation Dr. Golomb asked if the blocking antibody was effective when given after clear clinical onset of disease. Dr. Perrin replied that it did not work in this model, due to the severe degree of spinal cord inflammation at time of symptom onset. Dr. Golomb then commented on the difficulty presented by ALS and other human diseases which are

characterized by a delay between pathophysiological onset and clinical onset/detection. Dr. Perrin replied by stating his belief that ALS diagnosis would be a lot more aggressive and occur earlier if an effective therapy existed in the clinic and if better diagnostic biomarkers existed.

Dr. Golomb then asked if patients with superoxide dismutase (SOD) mutations were more likely to show the co-stimulatory pathway increase in gene expression. Dr. Perrin replied that this was not the case, and that this pathway was similar in familial and sporadic ALS.

Dr. Buchwald then asked Dr. Perrin if there was a tissue bank for ALS. Dr. Perrin replied that there were a few, including a biobank at the VA, a collection at his research institute (ALS TDI) and smaller collections such as the one that is at the University of Pittsburgh.

Chairman Binns then asked Dr. Perrin to repeat the significance of one his last slides on standardized pre-clinical development (PD) design (see Appendix A – Presentation 5). Dr. Perrin explained that his research institute made a conscious decision about a year and a half ago to start the PD studies a little before or in parallel with the efficacy studies in order to overlay findings across the different types of studies thereby enabling the researchers to better determine what the drugs were doing in the biological system. Dr. Perrin remarked that this approach prevents potentially effective treatments from being discarded due to selection of an incorrect dose in the efficacy trials.

Dr. O'Callaghan then asked about the activity of the CD40L antibody, and whether the observed glial fibrillary acidic protein (GFAP) decrease was a reflection of neuroprotection and lack of gliosis or whether there was an anti-inflammatory component to its action. Dr. Perrin replied that the drug (CD40L antibody) was administered via intraperitoneal (IP) injection (into the body cavity) and that it did not get into the CNS. He believes that the drug exerts its effects by decreasing the activation of cross-talk between the antigen-presenting cells, possibly in the periphery, and by blocking those lymphocytes from crossing the BBB into the CNS. He added that by not crossing the BBB, the lymphocytes are probably not able to activate microglia, thus freeing up the astrocytes to protect the neurons. He added that this CD40L antibody had also been effective in reducing amyloid beta plaque loads in a mouse model of Alzheimer's disease, though the implications of this action (and its effect on tangles) has yet to be determined. Dr. O'Callaghan then asked if the drug decreased gliosis. Dr. Perrin replied that it knocked down astrocytosis but its effects on microglial activation had yet to be investigated.

Dr. Sullivan then thanked Dr. Perrin and opened the discussion between Committee members and the morning's speakers.

Committee Discussion with Previous Presenters

Dr. O'Callaghan remarked that he felt Dr. Perrin's results regarding the CD40L antibody reflected on the potential complexity of Gulf War Illness, especially given the lack of knowledge regarding whether neuroinflammation is cause or consequence. He then asked Dr. Perrin for advice on how to proceed with identifying biomarkers. Dr. Perrin replied that he had previously served as head of biomarker development at Biogen and Aventis, and that biomarker development was very challenging. He then remarked that he had no doubt that

neuroinflammation was not the cause of ALS, but rather the immune system's reaction to things going awry – probably signaled by the dieback of nerves at the neuromuscular junction. Dr. Perrin recommended that a first line set of therapies for Gulf War Illness might resemble those for ALS, in that they would target the processes by which the immune system is attacking the CNS. He acknowledged that this would not be a cure, but that it would slow the disease progression while other drugs could be developed.

Dr. O'Callaghan then remarked on the difficulty of separating physiological inflammatory response from disease, in addition to separating cause for 20-year duration. He continued, commenting that there was a physiological basis for inflammation that was part and parcel of what the CNS responds to, and that the point at which that transitions from an acute resolvable response to something that goes chronic and becomes degenerative and debilitating was not known. Dr. Steele followed up on Dr. O'Callaghan's comment by stating that an inflammatory response has beneficial qualities, but that when something goes awry such that it cannot be turned off this chronic condition becomes problematic. She then asked Dr. Perrin if his research looked at the normal down-regulation of the response (in this case inflammation) that is somehow absent in the diseased state (for example, ALS), and whether those pathways were amenable to this approach. Dr. Perrin replied by noting that comprehensive profiling and comparison of other animal models have been useful in his research. He also commented on the importance of having a comprehensive picture of what various drug treatments are doing and how they might be tweaking the disease at hand.

Dr. Sullivan then asked whether Dr. Perrin had much experience with or knowledge of TLR antagonists being used to control inflammation. Dr. Perrin replied that TLR2 and TLR4 on various cell types were both highly upregulated in ALS (increasingly so as the disease progresses). He stated that he had not tried targeting that pathway yet due to a lack of good reagents for chronic use in animals. Dr. Sullivan commented on the pharmaceutical industry's perspective of the relatively small population of ill Gulf War veterans, and the similar "orphan" status of ALS, and then asked Dr. Perrin if he had any recommendations for how to garner the pharmaceutical industry's interest. He replied that the industry was very difficult to approach until phase 2 data had been acquired. Dr. Perrin then recommended that the Committee keep on top of the research coming out of the neurological disease field (e.g. ALS, Alzheimer's disease, frontotemporal dementia) and the immune field (e.g. lupus), noting that any promising treatment identified for these disease indications could potentially be repurposed into GWI research, given that the safety profile was alright.

Dr. Steele then asked Dr. Beaulieu if she knew what one might expect to find with regard to coagulation in a brain experiencing inflammation. Dr. Beaulieu replied that the coagulation pathway and platelets regulate clot-formation. In the event of low-level inflammation, Dr. Beaulieu remarked that she would expect to see an increase in cytokines present, which could cause malfunction of many cells. Dr. Steele asked if Dr. Beaulieu was aware of any researchers studying low-level micro-clotting, and whether thicker blood would be expected to be found in the brain as it was in the periphery under such conditions. Dr. Beaulieu replied that she was unaware of thickened blood being a symptom of prolonged states of inflammation, but rather that such a condition could be characterized by the continuous forming and breaking apart of small

clots, which in turn would be capable of consuming coagulation proteins in the blood such that the body might become hemorrhagic and unable to respond to any major damage that occurs.

Dr. White then introduced Dr. David Sherr, an immunologist who is a member of the BU Advisory Committee to the Committee, and asked if he had any comments on the morning's presentations. Dr. Sherr remarked that the inflammatory response is so complex that it is difficult to pin down. Dr. Sherr then addressed Dr. Steele's question about the component of the immune system whose role it would be to shut down the inflammatory response. He stated that several research studies of MS have found that regulatory T cells (which are up-regulated in ALS and would normally be expected to shut down the inflammatory response) appear to not be functioning well or at all in the CNS. Dr. Sherr was unaware of any research looking at whether this might be the case in Gulf War Illness. He added that several of the environmental chemicals to which Gulf War veterans were exposed have been shown to impact regulatory T cells in model systems. Dr. Sherr stated that these findings constitute circumstantial evidence sufficient to suspect that there is an undesirable modulation of these down-regulators of inflammation. Dr. Steele then asked how relevant these findings were to the brain. Dr. Sherr replied that the only way to know would be to investigate what the regulatory T cells were doing in situ, in the CNS. Dr. Golomb then remarked on the phenomenon by which clots formed in the periphery could make their way into the brain, as in the case of atrial fibrillation-induced strokes.

Dr. Meggs then commented on the anecdotal experience of many veterans who appear to be on a plateau of smoldering, non-progressive illness. He then posed the question of whether those who developed ALS could be "falling off" the plateau in a particular direction, while others might fall off in different directions, perhaps progressed by subsequent exposure events. Dr. Meggs then called on Alison Johnson, an author who has written extensively about multiple chemical sensitivity, to speak about a case who had experienced such a "second hit" phenomenon. Ms. Johnson then discussed the cases of two individuals who developed ALS and each avoided pesticides and other chemicals and survived for over a decade (far longer than average). She then expressed interest in seeing a study of whether patients who began avoiding chemicals after diagnosis prolonged their survival. Dr. Golomb then remarked that high cholesterol was one factor known to be linked to longer ALS survival.

Dr. Sullivan commented on Dr. Meggs' observation that some ill veterans appear to plateau while others develop neurological diseases, remarking that this was the reason she had posed the question of whether genetic polymorphisms might be contributing to illness trajectories. Dr. Meggs then stated that he had once seen an ALS patient who had been exposed to polychlorinated biphenyls (PCBs) and other chemicals as an employee of a utility company whose condition plateaued after he left his job.

Dr. Kenneth Jeffrey Myers, a former occupational health physician and invited speaker at the meeting, then asked Dr. Golomb if she knew what type of cholesterol had been linked to longer ALS survival. Dr. Golomb replied that cholesterol levels were higher on average in ALS patients, and that she believed this was probably a sign of an adaptive up-regulation. She added that among ALS patients, having higher cholesterol predicts significantly longer survival. Dr. Perrin then remarked that the link between cholesterol and ALS survival was still being debated, and that he had recently seen posters by two respected research groups refuting the association.

Chairman Binns then asked Dr. Sullivan to comment on the research regarding the interaction between toll-like receptors and gastrointestinal disease. Dr. Sullivan remarked that irritable bowel syndrome (IBS) and other diseases of inflammatory nature appear to have an association with TLRs, and asked if Dr. Beaulieu knew anything further. Dr. Beaulieu confirmed that TLRs appeared to be up-regulated in such diseases. She said that her research suggests that TLR4 does not have the same response in platelets as seen in TLR2, and that another group in Toronto has found TLR4 to act more like a primer. Dr. Sullivan then remarked that she had read about TLRs being associated with rheumatoid arthritis (RA) and asked Dr. Beaulieu if she knew much about that, particularly with regard to pain. Dr. Beaulieu was not very familiar with that, beyond what Dr. Sullivan had read. Dr. Sherr then remarked that RA is characterized by the production of autoantibodies which bind to DNA and get endocytosed into the cell, where they activate TLRs.

COL Marguerite Knox, a member of the Committee and a Gulf War veteran, spoke about her personal experience with repeated upper respiratory infections that occurred for many years following her Gulf War service. She said that eventually she had immunological studies run, which found that she had no B cells. She remarked that her family had a history of autoimmune diseases (lupus, RA) and hypothyroidism, and that she had experienced an adverse reaction to the live smallpox vaccine as a child. COL Knox then asked if her experiences demonstrated the type of cross-talk between innate and adaptive immune systems that Dr. Perrin's research is trying to prevent. Dr. Perrin replied affirmatively.

Chairman Binns then asked Dr. Perrin if he had any general advice for how research should be conducted to optimize progress in these areas, as VA was currently in the process of creating a new large program to address Gulf War Illness. Dr. Perrin replied that data tracking and sharing was very important. He also expressed the importance of negative data and lamented the fact that academic journals rarely publish it, and as a result research gets done that wastes time and money. Dr. Golomb concurred that this was a highly significant point, and suggested that the NIH should set up a repository for studies and a publication site where reviews could be submitted, along with reviews of the reviewers.

Dr. Sullivan thanked everyone for participating in the discussion, and then Chairman Binns dismissed the Committee for lunch. At 1:30pm the Committee reconvened with Dr. Sullivan's introduction of Dr. Christopher (Kit) Brady and Dr. Neil Kowall.

Gulf War Brain Bank Update

Dr. Christopher (Kit) Brady, VA Boston Healthcare System
Dr. Neil Kowall, VA Boston Healthcare System

Dr. Brady began the presentation by discussing the VA's ALS biorepository (VAB) brain bank (see Appendix A – Presentation 6). He explained how the VAB brain bank was initiated in 2006 by the VA Cooperative Studies Program following a request by the Scientific Advisory Committee of the VA ALS Registry before providing an overview of the enrollment and collection procedures.

After Dr. Brady's overview of the VA brain bank, Dr. Kowall presented on the connection between chronic traumatic encephalopathy (CTE) and ALS, findings that highlight the potential of the brain bank (see Appendix A – Presentation 7). Dr. Kowall explained that although CTE did not directly relate to GWI, his presentation demonstrated an example of how early exposure can lead to a chronic progressive disease (such as GWI).

Dr. Golomb proposed an alternative hypothesis for why football players in America and soccer players in Europe have been found to be at elevated risk of ALS. She postulated that the increased risk could be due to their exposure to herbicides used to maintain the grass fields. Dr. Kowall expressed interest in comparing such individuals with those who play only on artificial turf. Dr. Golomb replied that those fields may have elevated levels of lead, which has also been associated with increased risk of neurodegenerative conditions.

Dr. Meggs then asked if the brains of individuals suffering from toxic leukoencephalopathy had been studied in a similar manner. Dr. Kowall replied that the main difference between CTE and toxic leukoencephalopathy appeared to be that in many cases of CTE there was a long latency period between the traumatic event and presentation of cognitive deficits.

Dr. Buchwald remarked that she was reminded of David Snowdon's study of Alzheimer's disease and dementia in a group of nuns. She was impressed by the atmosphere of engagement in his scientific endeavors and stated that she saw potential to do that with the VAB brain bank. Dr. Buchwald said that the other thing that struck her was the importance of enrolling individuals that don't appear to be diseased. Dr. Kowall agreed that developing good relationships with veterans would be important.

Dr. Steele then asked if any brains had been collected from Gulf War veterans. Dr. Kowall stated that he did not think so. Dr. Brady then asserted that tissue had been obtained from one Gulf War veteran, though he did not know how many Gulf War veterans were currently enrolled. Dr. Steele asked if that one Gulf War veteran had been an ALS patient, and Dr. Brady confirmed that to be the case. Dr. Steele then asked if all current contributors to the brain bank had been ALS patients and again Dr. Brady asserted that to be true. Dr. Steele then asked whether future tissue samples would be collected from Gulf War veterans suffering from other neurological conditions. Dr. Brady replied that the VAB brain bank had submitted an expansion proposal to the VA central office and was currently waiting for its review to be completed. Dr. Steele asked what conditions Dr. Brady was hoping to then be able to include and he responded that he would like to see the development of a much broader bank of CNS and non-CNS tissues, to which any Gulf War veteran could contribute. Dr. Steele asked if there was any inventory of possible chemical exposures and injuries over the participating veterans' lifetimes. Dr. Brady replied that such information would be in the ALS Registry data, but that he did not know the extent of the information therein. Dr. Steele then asked for clarification regarding the level of data collection that the VAB brain bank was doing, and Dr. Brady explained that a substantial amount of data came from the ALS registry, but that the VAB brain bank did not conduct some follow-up data collection to track disease progression from onset. He added that there had been a bit of a gap between the time that the ALS Registry closed and stopped follow-up and when the VAB brain bank had been able to transfer and reinstitute the correct active follow-up protocol.

Dr. Steele then asked for clarification regarding the status of the ALS Registry. Dr. Bill Goldberg, the Committee's designated federal officer, expressed his belief that the ALS Registry was still active, noting that it was still receiving funding. Dr. Brady replied that they were no longer doing active follow-up. Dr. Sullivan then asked if the ALS Registry was recruiting new cases. Dr. Brady replied that it was not.

Dr. Steele then asked what kinds of study proposals were requesting the use of the VAB brain bank tissues, and what kinds of studies were actually being done with the tissues. Dr. Brady replied that no active studies were yet underway because they had just reviewed the first batch of tissue requests. He added that these requests were currently under review at the VA central office prior to any release of tissues. Dr. Sullivan then asked if the tissues were being fixed in a way that would allow investigation of glial pathology. Dr. Brady replied that one hemisphere of each brain was frozen and the other was formalin-fixed and embedded in paraffin. He stated that Tina Trevor was the technical person who might be able to more directly answer Dr. Sullivan's question. Dr. Sullivan then asked if the tissue requests need to come from VA investigators or if outside researchers could also make requests. Dr. Brady replied that anyone could request tissue.

Dr. Steele then asked if there were samples of blood or cerebrospinal fluid being held at the VAB brain bank. Dr. Brady replied that blood had been collected through the ALS Registry, and it was being stored at the VA central biorepository, but that some individuals declined to donate blood. He said that he thought the VAB brain bank also had blood samples stored for the majority of cases. Dr. Sullivan then recommended that as the VAB brain bank thinks about enlarging their program to include Gulf War veterans with other illnesses, they consider brain cancer because many reports had been coming in to the Committee office about Gulf War veterans dying from brain cancer. Dr. Steele then asked if the VAB brain bank had consulted with members of the Gulf War Illness research community in order to decide on priorities regarding tissue sampling and preservation. Dr. Brady said that the VAB brain bank had been collaborating with a number of individuals at developing Gulf War programs, including Dr. Dawn Provenzale at the Durham VA, as well as Dr. Susan Proctor. He added that broad sampling of tissues from all major organ systems, including muscle and bone, was being considered. In addition, he commented on the clinical complexities inherent to Gulf War Illness, and stated that he was working with multiple stakeholders to determine how best to combine pre-existing data from various sources (Department of Defense data as well as data collected through the Gulf War Registry exam, for example) with new/ongoing data collection on a national scale.

Mr. David Lee, a Gulf War veteran from the audience, stated that he would like to see the VAB brain bank facilitate studies of Gulf War veterans and the causes of their mortality.

Dr. Sullivan encouraged Dr. Brady to reach out to other existing cohorts of Gulf War veterans in the VAB brain bank's efforts to conduct follow-up data collection.

MAJ Nichols expressed her frustration that the Gulf War veterans had been calling for a brain bank for many years, and that no studies on brains from Gulf War veterans (with ALS or otherwise) were underway. She added that she also would have liked to see the inclusion of Gulf War veterans with other neuroimmune conditions (including MS).

Chairman Binns then commented that he felt it was disconcerting that these funds continued to be recorded as Gulf War Illness funds even though the VA had only just begun to commit to looking at Gulf War Illness. Dr. Steele then remarked that the issue was an ongoing one, noting that of the 6500 or so veterans in the ALS Registry, about 100 were Gulf War veterans.

Dr. Sullivan then thanked Drs. Brady and Kowall and introduced the next speaker, Dr. Anne Louise Oaklander.

Small-Fiber Polyneuropathy: A Potential Contributor to GW Illness

Dr. Anne Louise Oaklander, Massachusetts General Hospital
Dr. Max Klein, Massachusetts General Hospital

Dr. Oaklander began by introducing Dr. Max Klein before presenting an overview of neuropathic pain, small-fiber polyneuropathy (SFPN), and the potential connections between small-fiber nerve damage and Gulf War Illness (see Appendix A – Presentation 8). Dr. Oaklander stated that although some preliminary evidence of autonomic abnormalities is consistent with SFPN, previous studies of polyneuropathy in Gulf War veterans have not looked at small-fiber damage. She then described the methodologies that she uses to diagnose SFPN and to study pain. Dr. Klein then presented on the autonomic function testing methodologies being used to aid in the diagnosis of SFPN (see Appendix A – Presentation 8). He then discussed the plan for a project he is working on with Dr. Oaklander. One of the two major goals of the project would be to identify the best tests to detect small-fiber nerve damage. He explained that the second aim of the project would be to use the best of those tests to determine the prevalence of SFPN among veterans with GWI, and to compare that rate to the prevalence of SFPN in unaffected Gulf War veterans and civilian controls. Dr. Oaklander then wrapped up the presentation by briefly discussing a case study of a young man with SFPN triggered by an autoimmune response, which she remarked could be occurring (or have occurred) in active duty troops, potentially accounting for adverse effects in the central and peripheral nervous systems.

At the conclusion of the presentation, Dr. Golomb asked if some of the effects in young people attributed to autoimmune diseases might be induced by toxins or toxicants. Dr. Oaklander replied that there was no history of toxic exposures in all but perhaps one case that she had seen in teenagers, and that autoimmune markers were detected in these individuals.

Dr. Steele then remarked that some small fiber and a lot of autonomic nervous system function research that was not cited in Dr. Oaklander's presentation had been done in Gulf War veterans. Dr. Oaklander replied that she was familiar with the findings presented in the Committee's 2008 report, Gulf War Illness and the Health of Gulf War Veterans, and that she was a reviewer for the recent Institute of Medicine (IOM) report on the Health Effects of Serving in the Gulf War (Volume 8). Dr. Steele then commented that there had been at least 10 studies of autonomic functioning, 4 of which looked at Valsalva maneuvers, none of which showed anything, while at the same time tilt-table testing showed quite a lot. Dr. Steele added that Holter monitoring also had been useful, while most of the other autonomic function testing methodologies had not been. Dr. Oaklander replied that she had tried to show the results of the research in her slides, but that the findings had been mixed. Dr. Steele replied that it was not difficult to characterize which tests showed something and which did not. She then asked about the findings of one previous

study in which a Doppler test was done to look at vasodilation in the skin using acetylcholine infusion. Dr. Golomb replied that she recalled the results of that research showing that Gulf War veterans were similar to OP-exposed individuals but differed from individuals with chronic fatigue syndrome (CFS). Dr. Oaklander agreed, and explained that she was aware of the previous work that had been done, but felt justified in her research since she planned to test the same patients using different autonomic function testing methodologies.

Dr. Buchwald then asked how epidermal nerve fiber (ENF) density was quantified and what the intra-observer reliability (or reproducibility) of those readings was. She also asked how Dr. Oaklander reconciled the picture of multiple neuropathy with the multitude of functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) studies that seem to indicate that central sensitization was the mechanism underlying at least fibromyalgia and chronic widespread pain. Dr. Oaklander replied that the number of nerve endings was counted under a microscope in tissues prepared using free-floating immunohistochemistry then fixed to slides. She also said that her lab was mandated to check on intra-observer reliability because of its status as a JCHO-accredited clinical diagnostic lab, and that it was 99% at last check. Dr. Oaklander then addressed Dr. Buchwald's second question by stating that the CNS changes experienced by individuals suffering from chronic pain contribute to the overall level of disability and malfunction that the patients have, but that the changes are nonspecific. Moreover, Dr. Oaklander explained that the presence of changes in the brain (as revealed by imaging studies) does not mean that the changes that are detected are the primary site of pathology. She then gave several examples, including irritable bowel syndrome, and explained that in the case of fibromyalgia it was becoming increasingly clear that some observed CNS changes are markers for other comorbid issues such as depression, disuse and disability and use of medications.

Dr. Golomb then asked about inter-reader variability on the same sample, as well as the test-retest variability in Dr. Oaklander's lab, commenting on one of her patients who had electromyogram (EMG) and nerve conduction velocity (CV) testing done twice but abnormalities detected only once. Dr. Oaklander replied that for EMG and CV studies the test-retest usually changes because they are done at different points of the disease progression, especially for illnesses like ALS. For the skin biopsies, Dr. Oaklander said her lab had very good "between-punch" variability if the biopsies were done at the same time and place on the skin (the standard used across the world is 10cm above the ankle on the outside of the leg). Dr. Golomb followed up by asking if that standard distance from the ankle was appropriate for individuals of differing heights. Dr. Oaklander replied that her lab was currently looking into that, as well as the impact of patient weight on normal innervation.

Dr. O'Callaghan then asked if the incidence of small-fiber neuropathy was increasing among young civilians or if better diagnosis was just picking up more cases. Dr. Oaklander replied that this was not known, and that no good population-based data existed regarding the incidence of SFPN. She said that the number of people living with diabetes or HIV (both of which are driving factors behind the occurrence of SFPN) was on the rise, and added that one recent study suggested that, independent of diabetes, obesity alone may be a predictor of SFPN.

Dr. Meggs then asked if Dr. Oaklander's lab processes specimens from other institutions. Dr. Oaklander replied that there was a commercially-available lab, Therapath, that could process skin punches in this manner.

Dr. Steele then asked if any research like that which Dr. Oaklander is proposing for Gulf War illness has been done in fibromyalgia or chronic fatigue syndrome. Dr. Oaklander replied that the definitive study on fibromyalgia had not yet been done, though she said that there is some evidence of peripheral abnormalities in the cutaneous nerves of fibromyalgia patients. Dr. Oaklander then remarked that every patient her lab has diagnosed with SFPN has stated that they have fibromyalgia, and as such she feels the term fibromyalgia is used as a catch-all phrase for anyone experiencing widespread unexplained chronic pain, and that some proportion of them have SFPN, which (unlike Gulf War Illness of fibromyalgia) has a defined neuropathology associated with it, as well as a list of treatable causes. Dr. Oaklander then offered a disclaimer, stating that she did not believe Gulf War Illness arose from one single cause, or that all ill Gulf War veterans had abnormalities in their skin nerves, but that she suspects a subset of ill Gulf War veterans may, and that identifying them could lead to the identification of helpful treatments.

Dr. Sullivan acknowledged that Dr. Oaklander was just beginning to recruit for her study, but asked if she could talk about her inclusion and exclusion criteria. Dr. Oaklander replied that she was interested in studying all patients with Gulf War Illness, though different criteria were in place to separate symptomatic from asymptomatic individuals. She said she also hoped to be able to network with researchers and veterans groups in order to tap into existing cohorts of Gulf War veterans. Dr. Sullivan asked if Dr. Oaklander was just doing broad outreach, and Dr. Oaklander replied that she had just barely begun the recruitment process, as the start date had been cleared only two months prior.

Dr. Dane Cook, a researcher studying chronic musculoskeletal pain in Gulf War veterans, asked if Dr. Oaklander could tell by looking through the microscope whether fibers were sympathetic fibers involved in cardiovascular control, for instance, or nociceptors, or whether this distinction didn't matter in the terms of SFPN. He then asked whether Dr. Oaklander thought that her findings would translate to small fibers innervating muscle. Dr. Oaklander replied that there was a lot of overlap between autonomic function and nociception in small fibers. She explained that the common conception of a separate autonomic and somatic nervous system was incorrect, and that the same single axon which may be a sensory receptor for perhaps several sensory modalities at the same time could be interacting with the immune system and the vascular system, and as such they are really polymodal cells. Dr. Cook followed up by asking if Dr. Oaklander had considered looking at the influence of either physical activity behaviors or fitness. Dr. Oaklander replied that she had not, but was intrigued by the idea.

Chairman Binns then asked Dr. Oaklander if she had any thoughts on the suggestion made by another researcher, Dr. Abou-Donia, that there may be delayed central nervous system effects analogous to the OP-induced delayed neuropathy (OPIDN) seen in individuals exposed to large doses of OP agents. Dr. Oaklander replied that due to their lack of a myelin sheath many of the small fibers were differentially vulnerable to many toxins and toxicants, and may be the first nerve fibers to experience damage from some diseases or conditions that can progress to affect other nerve fibers. Dr. Golomb then restated Chairman Binns' original question, asking if there

were any processes analogous to OPIDN in the small fibers. Dr. Oaklander replied that the concept of small fiber neuropathy has come out of the diabetic neuropathy community and has been extended to HIV and chemotherapy, to a certain extent, but that it hasn't really been meshed with the neurotoxicology work as it should be.

Dr. Sullivan then thanked Dr. Oaklander and Dr. Klein before Chairman Binns called for a brief break. At 3:25 the Committee reconvened with Dr. Sullivan's introduction of Dr. Jeffrey Mogil.

The Nature and Nurture of Pain

Dr. Jeffrey Mogil, McGill University

Dr. Mogil discussed current findings and approaches to studying the role genetics play in chronic pain states and variability in human pain sensitivity before addressing some of the findings that have arisen from his laboratory's linkage mapping research (see Appendix A – Presentation 9). In his presentation, Dr. Mogil stated that heritability of pain traits (what he termed the genetic architecture of pain) was similar across studies of clinical pain states, experimental pain states in humans and pre-clinical pain states in animal models. He felt that the genetic contribution was slightly less than 50 percent. Dr. Mogil also talked about the existence of qualitative sex differences in pain processing, namely the apparent sex-specific involvement of TLR4 receptors in pain processing pathways in the spinal cord. He remarked on the large number of pain-relevant genes, many of which have yet to be identified. Dr. Mogil then stated that the identification process and the incorporation of genetic data into pain treatment would take considerable time.

At the conclusion of Dr. Mogil's presentation Dr. Meggs remarked that in addition to genes and the environment, luck plays a role in trait variability. Dr. Mogil agreed that luck plays a certain role, but that genes and other factors do contribute to real differences in pain sensitivity.

Dr. Golomb then commented that there were also environmental effects on gene expression. She added that the mitochondrial genome should be considered in the study of chronic pain. Dr. Mogil replied that Dr. Gary Bennett and others were currently studying mitochondrial roles in pain.

Dr. Sullivan thanked Dr. Mogil before introducing the last speaker of the day, Dr. Dane Cook.

Psychobiology of Pain and Exercise in Gulf War Veterans with Chronic Musculoskeletal Pain

Dr. Dane Cook, William S. Middleton Memorial Veterans Hospital

Dr. Cook presented his research regarding how exercise alters pain symptoms, pain sensitivity and brain structure and function in Gulf War veterans with chronic musculoskeletal pain (CMP) (see Appendix A – Presentation 10). Dr. Cook's previous research suggested that the CNS of Gulf War veterans with CMP were not properly regulating sensory information, and that these individuals became more sensitive to pain stimuli following an acute bout of exercise. Dr. Cook has also used fMRI to show that Gulf War veterans with CMP exhibit augmented brain responses to both non-painful and painful sensory stimuli even in the absence of exercise. During

his presentation, Dr. Cook also discussed some findings from his current imaging research investigating the cognitive modulation of pain in patients with fibromyalgia. He concluded by presenting the study design for his recently funded study which will involve the impact of resistance exercise training (as a treatment) on pain and brain structure and function in Gulf War veterans with CMP.

Dr. Golomb then suggested that the CNS differences Dr. Cook's research found could be due to abnormalities or effects occurring in the peripheral nervous system. Dr. Cook agreed, stating that he was simply suggesting cognitive modulation as one mechanism of pain maintenance. Dr. Golomb then asked if the healthy Gulf War veterans (those that did not report experiencing CMP) exhibited exercise-induced hypoalgesia (EIH), as expected. Dr. Cook replied that these healthy veterans did not experience EIH (decreased sensitivity to pain immediately following a bout of exercise). He noted that his study participants were older and perhaps less physically fit than the college-age subjects of most EIH research, and further contextualized the findings of his research by explaining that pain sensitivity increases with age and that pain modulation decreases with age. Dr. Golomb then suggested that Dr. Cook include a non-exposed non-symptomatic control group in his next study. Dr. Cook agreed that this was a good suggestion, and that he would like to have two control groups – one composed of healthy veterans and the other of healthy civilians.

Dr. Meggs then asked if Dr. Cook had monitored for the amount of fatigue that the exercise induced in the different groups. Dr. Cook replied that he had looked at fatigue, and that there was no significant symptomatic exacerbation of fatigue in the Gulf War veterans with CMP immediately following exercise. He added that he had not looked at physiological skeletal muscle fatigue.

Dr. Steele then asked for clarification on how the cases and controls were defined, specifically inquiring about whether the cases were defined solely by the presence of chronic widespread pain. Dr. Cook replied that many of the cases likely had other symptoms as well, adding that of the individuals evaluated at the War-Related Injury and Illness Centers (WRIISCs), 100 percent of those who had chronic fatigue had chronic pain, but that the converse was true in only about 75 percent of patients. Dr. Steele then asked if the reported fatigue could have arisen from injury in any of Dr. Cook's study participants. Dr. Cook replied that he had conducted a very robust clinical assessment to screen out individuals with past injuries, and stated that the cases had to be experiencing medically unexplained widespread musculoskeletal pain. Dr. Steele then asked if Dr. Cook had assessed other symptoms. He said that he had looked at fatigue, and that in the upcoming treatment study he planned to look more closely at pain as well. Dr. Steele then asked whether the individuals in the control group included anyone with symptoms other than chronic unexplained pain. Dr. Cook replied that the control group consisted of healthy Gulf War veterans.

Dr. Sullivan then asked if Dr. Cook had considered looking at inflammatory markers. He replied that he already had, but that no robust changes were seen in IL-1 or IL-6, though some interesting findings regarding IL-10 were still being interpreted. Dr. Sullivan asked if Dr. Cook had seen Dr. Nancy Klimas' recent work on immune network remodeling. Dr. Cook said that he was very familiar with that research and had talked with Dr. Gordon Broderick (Dr. Klimas' co-

investigator) about it, but Dr. Cook said he was not sure he had a large enough sample size or enough time points to apply the network modeling to his own dataset. He added that he did plan to do it for his upcoming study.

Dr. Sullivan then asked Dr. Cook how his study would be different from a previous exercise treatment trial in Gulf War veterans (conducted by a different group of researchers) which found that exercise was not helpful to veterans with Gulf War Illness. Dr. Cook replied that the previous study had actually looked at the effects of acute exercise rather than resistance exercise training, which is what his study would assess. Dr. Cook stated that unlike the previous study (which ran for 12 weeks, during which the participants exercised a median number of 6 times), his study would involve one-on-one training at the VA a couple times per week as well as monitoring of independent physical activity outside of the VA. He added that there would also be a detailed plan to attempt to improve adherence.

Dr. Steele then asked if Dr. Cook was concerned about the fact that exercise induced hyperalgesia (increased sensitivity to pain) in ill Gulf War veterans, according to his previous research. Dr. Cook said that he was, and that he was interested in finding out where (temporally) exercise changes from an acute, noxious, illness-exacerbating stimulus to an efficacious treatment. He explained that exercise had a clear beneficial impact on patients with fibromyalgia, and so he would expect to see similar effects in Gulf War veterans with chronic pain.

Dr. Sullivan stated that she felt Dr. Cook's hypothesis was worthy of trial. She then remarked on the experience of a Gulf War veteran who had been suffering from severe pain which was exacerbated when he rode his bicycle for exercise. She explained that this veteran had continued biking despite the very intense pain and that eventually his pain subsided. Dr. Cook responded by explaining that the resistance exercise training in his study would involve very low intensity exercise, the level of which would be standardized but also based on each individual's responses.

Dr. Golomb then commented that exercise was one of the few things known to increase the body's number of mitochondria. Dr. Cook remarked that this effect was known as adaptation to exercise.

Chairman Binns asked if any of the veterans present had comments to make based on their experience with exercise. No one had any comments, so Chairman Binns and Dr. Sullivan thanked Dr. Cook and opened the floor to public comments.

Public Comments

Mr. David Lee, a Gulf War veteran, asked if anyone present had experience or knowledge with knee problems related to the loss of cartilage. Dr. Steele replied that it had not been looked at in any studies, but that she was aware of some arthritis-related knee problems in Gulf War veterans. Mr. Lee stated that quite a few members of his unit from the Gulf War had undergone knee surgery. Dr. Sullivan agreed that she had heard many veterans complain of knee problems but that there had been no good scientific studies.

SSG Ed Bryan, a Gulf War veteran, commended the Committee for their continued research into Gulf War Illness but expressed concern that, to his knowledge, the Committee had not looked at the military nerve agent book provided to the commanders in the Gulf War (field manual 8-285). He explained that the manual had been completed in February of 1990, but he stated that the Department of Defense (DoD) had then removed a lot of detailed information in 1996. He expressed his belief that some of the information that the DoD had removed would be useful to the Committee in its efforts to hone the research. SSG Bryan also said that he was being seen by a nurse practitioner at his local VA but that she and the general physician were not knowledgeable about Gulf War Illness. He requested that the VA make consultations with neurologists and environmental physicians possible for ill veterans such as himself. SSG Bryan then expressed the need for accurate death rate data for the Gulf War veteran population. He also commented on the potential benefits of alternative therapies such as acupuncture, exercise, and healing rocks. Lastly, SSG Bryan asked if studies had been done to determine whether any deaths or illnesses among Gulf War veterans were due to diseases common to the Gulf War theater.

Dr. Steele replied that she had looked at the early version of the nerve agent field manual, and that parts of it had been incorporated into the Committee's 2008 report on Gulf War Illness and the Health of Gulf War Veterans. She said that there had been quite a few treatment and treatment-related studies of Gulf War veterans and that some results had already come out and others were forthcoming. Dr. Steele expressed her desire to see the treatment results presented together in a practical synopsis. Mr. Bryan said he hoped to see something informational put together for the veterans wondering what they could do to improve their health, particularly given the approaching 20 year anniversary of the end of the Gulf War. He emphasized the importance of having someone with medical expertise disseminate the information. Mr. Bryan then thanked the Committee for their time. In response, Chairman Binns expressed his frustration that many of the common sense activities that ill Gulf War veterans were doing in an attempt to improve their health (such as dieting or avoiding chemicals) were very difficult to study scientifically. He stated that he would like to enable veterans to educate each other about the approaches they have found useful.

MAJ Nichols stated that she was upset that the Committee's activities and the work of their invited speakers were not highly disseminated. She referred to the Chronic Fatigue Advisory Group's website (hosted by the Department of Health and Human Services), where meeting proceedings were broadcast live. She requested that the Committee do the same, keeping in mind the veterans who can't make it to meetings due to financial and/or health burdens. She also suggested that the Committee meet once a year in Denver or somewhere other than Boston or Washington DC that logistically makes sense, where new researchers could potentially be tapped or recruited. MAJ Nichols also expressed concern over the lack of many veterans' financial ability to travel to research sites in order to participate in important studies. She concluded by discussing potential environmental factors that had not yet been considered in the etiology of Gulf War Illness. MAJ Nichols spoke of a marine Gulf War veteran who was part of a unit that was put on the antibiotic ciprofloxacin for 40 days in theater. She then proposed that fluoride (which she claimed could be found in ciprofloxacin, sarin, depleted uranium, OPs, desalinated water, and some psychiatric drugs) be investigated with regard to Gulf War Illness.

At 5:12pm Chairman Binns thanked everyone for participating in the day's proceedings and adjourned the meeting for the evening.

DAY 2

At 8:33am Dr. Sullivan began the meeting by introducing the first speaker of the day, Dr. K. Jeffrey Myers.

Toxicogenomics Overview

Dr. K. Jeffrey Myers, Malcom Randall VA Medical Center

Dr. Myers reviewed several recent articles and current research in the field of toxicogenomics, which compares how toxic exposures influence expression of the genome (see Appendix A – Presentation 11). He began his presentation by describing the far-reaching genetic effects observed in rodents exposed to soman, sarin, and organophosphates (OPs). Dr. Myers stated that findings from the OP studies suggest that these agents can exert genetic effects via mechanisms other than acetylcholinesterase (AChE) inhibition. Dr. Myers then discussed a review article on the epigenetics of environmental lung disease and provided an overview of the known roles of TLRs in various human diseases. He also described ongoing research being conducted to seek the genetic basis of an individual's susceptibility to occupational hydrocarbon solvent neurotoxicity, as well as another current study which aims to identify and compare the genomic responses to various environmental toxicants across different species. Dr. Myers concluded by remarking that there is still much that is unknown in the toxicogenomics field.

Dr. Sullivan thanked Dr. Myers for his overview, and commented on the significance of the OP findings. She highlighted the fact that OPs can have other effects separate from AChE inhibition, and that research should look at whether these non-cholinergic effects could potentially lead to disease in vulnerable individuals exposed to OPs. Dr. Sullivan also said that she was struck by the fact that TLR polymorphisms might be associated with autoimmune diseases such as Crohn's disease and IBS. She expressed her desire to explore those potential associations in more depth since nothing was known about those possible susceptibilities in Gulf War veterans.

Dr. Golomb then re-emphasized the point about OPs acting via mechanisms beyond AChE inhibition. She stated that this was also supported by the findings of other research, including a study conducted by Dr. Samuel Pena-Llopis that showed large doses of antioxidants administered right before or right after OP exposure were protective against the morbidity and the lethal effects of the OPs. Dr. Golomb added that in an early toxicogenomic study conducted in rodents by Dr. Soreq, pyridostigmine (PB) exposure led to altered splicing of mRNA for AChE that was water-soluble and not localized near the synapse. Dr. Sullivan added that some OPs also impact mitochondria directly, causing reactive oxygen species (ROS). Dr. Golomb agreed, stating that there was a good review article on the subject authored by Dr. Milatovic. Dr. Sullivan added that toxicogenetic studies of OPs might also shed light on potential mechanisms by which OPs may have caused inflammation in ill Gulf War veterans.

COL Knox asked if Dr. Myers had identified any treatments or approaches that made ill Gulf War veterans feel better, and then asked him what he thought of his colleagues' knowledge of

Gulf War Illness at the VA Medical Center in Gainesville. Dr. Myers replied that there was a high degree of variability in the health of Gulf War veterans he saw. He said that many veterans were too ill to make their appointments, but others were getting by and trying various over the counter treatments. No particular medication came to mind when Dr. Sullivan asked Dr. Myers if veterans were reporting experiencing relief from any self-administered substances. He said that there was a lot of trial and error going on with treatments since the mechanisms of Gulf War Illness were not known. Dr. Myers said that his colleagues were tailoring treatments to each individual, and that he would advise individuals to continue doing anything that they found helpful.

Dr. Sullivan then thanked Dr. Myers before introducing the next speaker, Dr. Richard Clapp.

Epidemiology of Brain Cancer

Dr. Richard Clapp, Boston University School of Public Health

Dr. Clapp first defined the different types of brain cancer, then discussed the established risk factors as well as the potential occupational and environmental risk factors for adult onset brain cancer (see Appendix A – Presentation 12). One of the known risk factors Dr. Clapp discussed was high-dose radiation, and he also mentioned non-ionizing radiation as a potential occupational risk factor. Dr. Clapp also provided an overview of the 2009 study conducted by Drs. Barth, Kang, Bullman and Wallin that looked at neurological mortality of Gulf War veterans followed from 1991-2004. Though the study found no significant differences between deployed Gulf War veterans and non-deployed Gulf War era veterans overall, deployed veterans exposed to either the Khamisiyah weapons depot plume for two or more days or oil fire smoke had a significantly increased risk of dying from brain cancer compared to the non-exposed Gulf War veterans. Dr. Clapp added that Dr. Barth had communicated to him that the number of brain cancer deaths was low in the early years of the study but had increased in the latter years of the study (2001-2004). Dr. Clapp then remarked that the latency period between exposure and the development of brain cancer can be 20 to 30 years or more, and since the Gulf War exposures occurred 20 years ago he believes more cases may emerge in the next 15 years. Dr. Clapp expressed his belief that the results for Gulf War exposures to oil fires and the Khamisiyah plume warrant continued follow-up. He concluded his presentation by providing an overview of the research approaches being used to study the potential elevation of solvent-associated cancers among East Coast marines who were exposed to contaminated drinking water over three decades at Camp Lejeune in North Carolina. Dr. Clapp brought up this example because he thought it could serve as a possible model for studying cancer among Gulf War veterans. He added that the Central Brain Tumor Registry in Illinois would be an invaluable epidemiological resource for a nested case-control study of Gulf War veterans.

Dr. Golomb then asked if a wise approach to reducing the possible potentiating effect of non-ionizing radiation might be to suggest that veterans (and others) request protection for their brains during subsequent (medical) radiation procedures. She acknowledged that it might not make any positive difference, but that it almost certainly wouldn't hurt. Dr. Clapp replied that in May the president's cancer panel had concluded that people were being exposed to too much radiation, including from CT scans, and that better precautions needed to be taken.

Dr. Golomb then mentioned Ben Williams, a current faculty member at her university (UCSD), who developed a highly fatal form of brain cancer 15 years ago and then used findings from animal studies to devise highly-effective self-treatments, which he credited with saving his life. Dr. Golomb suggested that veterans who were interested in hearing more about his experience may want to contact him.

Dr. Steele then commented on the complicated exposures in the Gulf War, explaining that many exposures had to be elucidated from DoD maps. She expressed concern that the map of who was most likely to be exposed to depleted uranium (DU) in the Gulf War theater overlapped almost completely with the Khamisiyah plume map. She then asked if looking at the onset and types of tumors being seen in the 2009 neurological mortality study could reveal what types of exposures (i.e. OPs vs. radiation/heavy metals) may have caused the cancers being seen. Dr. Clapp responded by stating that humans are like animals let out of their cages, and that when exposures are comingled it becomes very hard to sort out which exposure or combination of exposures might be the cause of disease. He said that one way of getting at answers in these situations is to identify and look for disease in individuals known to only have been exposed to one predominant exposure. Dr. Clapp did not know of any group of Gulf War veterans only exposed to one agent, and thus he stated that conclusions must be inferred from other studies.

Dr. O'Callaghan asked whether prior inflammatory events (such as allergies or acute or chronic infections) contribute as risk factors to subsequent development of glioblastomas and astrocytomas in general. Dr. Clapp deferred to Dr. Sherr, who said that he did not know about brain tumors specifically, but that inflammatory events are risk factors for most other cancers. He said that this may be related to establishing a micro-environment of oxidative stress and an environment that suppresses the types of cells that keep the tumors under control.

Dr. Sullivan asked Dr. Clapp whether the latency period was such that brain cancer should still be a concern for Gulf War veterans. Dr. Clapp confirmed that more cases could be expected to emerge in the next 15 years. Dr. Sullivan responded by stating that she had heard from several Gulf War veterans at the RAC office who currently have or who recently passed away from brain cancer. She said that some of these veterans know that they were in the vicinity of the Khamisiyah plume or were tank commanders at the time (or both), and that this gave her reason to agree with Dr. Steele and to believe that there were probably overlapping exposures of concern that may be related to cancer development. Dr. Sullivan mentioned that in her study of approximately 150 Gulf War pesticide applicators, 2 non-cancerous brain tumors were detected (and successfully removed). She added that one of the tumors was a rare acoustic neuroma and the other was a meningioma. Dr. Sullivan emphasized the need for the VA to continue to follow the incidence of brain cancer in Gulf War veterans given that the expected latency period is still ongoing. She added that some of the veterans with brain cancer who had recently contacted her also had difficulty acquiring disability benefits from the VA, even after submitting multiple claims and appeals and that she was concerned that these veterans were having to fight for benefits while they were fighting for their lives.

Dr. Sullivan then introduced the next speaker, Dr. Lisa Conboy.

The Effectiveness of Acupuncture in Treating Gulf War Illness

Dr. Lisa Conboy, The New England School of Acupuncture

Dr. Conboy presented an overview of her recently-funded research study that aims to recruit a sample of veterans with Gulf War Illness and evaluate the effectiveness of an individualized acupuncture treatment protocol on the veterans' most distressing Gulf War Illness symptom (see Appendix A – Presentation 13). A secondary goal of her study was to gather data to better understand the mechanisms of Gulf War Illness. In her presentation, Dr. Conboy discussed the definition of Gulf War Illness that she was using, outlined the Gulf War theater toxicant exposures, and provided an overview of her study methodology. Dr. Conboy also talked about how Traditional Chinese Medicine (TCM) characterizes Gulf War Illness.

At the conclusion of Dr. Conboy's presentation, Dr. Buchwald asked several questions. She first asked Dr. Conboy to clarify her outcomes in the treatment and control groups. Dr. Conboy explained that her study was designed with power to detect an effect after 2 months of treatment, so the main study would compare ill veterans receiving 2 treatments per week for 2 months (group 1) to those who had been waitlisted (and not received any treatments) for two months (group 2). She stated that the study would also involve a secondary comparison that looks at the impact of dose, in that ill veterans receiving biweekly treatments for 6 months (group 1) would be compared to those receiving weekly treatments (group 2, which will receive weekly treatments for 4 months following the 2 month waitlist period). Dr. Buchwald then asked Dr. Conboy how she would measure her primary outcome. Dr. Conboy replied that she uses the SF-36 (a 36-question short form health survey) and looks at both mental and physical components of health. Dr. Buchwald asked what the participants are told when they are enrolled and assigned to a group. Dr. Conboy replied that each participant is told that they will receive real acupuncture during the course of the study, and it is made clear that 50 percent of the participants will be randomly assigned to a 2-month waitlist. Dr. Buchwald then recommended that Dr. Conboy measure expectations as part of the study. Dr. Conboy said that she planned to do that. Dr. Buchwald followed up by asking how Dr. Conboy planned to do so, since there was no standard way of measuring expectations. Dr. Conboy stated that there was a measure she had used in previous studies (the Mercer scale) that asks each participant to rate their expectations for symptom outcome on a 7-point scale at various stages of the study. Dr. Buchwald then asked how many patients each acupuncturist would be seeing as part of Dr. Conboy's study. Dr. Conboy replied that no cap had been set, so the limiting factor would be each acupuncturist's availability. She added that most acupuncturists worked no more than 40 hours per week and that each treatment for the study lasts an hour. Dr. Buchwald inquired as to whether there was any chance that the participants could meet in the waiting room and talk about their experiences to each other. Dr. Conboy said that it was possible. Dr. Buchwald remarked that in a similar study she had conducted she ensured that there was no overlap between participant visits. Dr. Conboy agreed that this was a good idea which she would try to incorporate into her study if possible, but that it might prove to be difficult since the participants would be scheduling their visits with the practitioners (not the study coordinators). Dr. Buchwald then asked whether all of the practitioners were trained in the same type of acupuncture. Dr. Conboy replied that they were, and that they all had diagnostic training in the 8 pattern principles, which she said was one of the more common TCM trainings in the US. Dr. Buchwald's last question was whether Dr. Conboy's study was powered to account for variation by practitioner. Dr. Conboy agreed that

this could be a weakness of the study design, but explained that she couldn't fully answer the question because the practitioners were still being recruited and trained.

Dr. Steele asked who the subjects were going to be and commented that the case definition for Gulf War Illness that Dr. Conboy had proposed was a modification of the Center for Disease Control (CDC) definition. She explained that the persistent fatigue lasting for 24 or more hours after exertion was actually only present in a subset of ill Gulf War veterans. That aside, Dr. Steele was curious to know whether Dr. Conboy was excluding individuals with other medical conditions (such as lupus). Dr. Conboy replied that she was not excluding people with other medical conditions. Dr. Steele expressed concern that doing so could muddy the waters regarding what type of treatment each individual gets, as well as what outcomes would be seen. Dr. Conboy remarked that she had intentionally aired on the side of being inclusive in her study design. She added that many ill Gulf War veterans have multiple symptom complaints, including those that fall outside of Gulf War Illness. Dr. Steele again voiced her concern that the primary question of whether the acupuncture and TCM treatments work for this spectrum of illness would not be answered. Dr. Conboy suggested that using quality of life as a general outcome measure would address part of Dr. Steele's concern. Dr. Steele countered that positive changes in quality of life among the broad array of participants would not reveal whether the treatments could help the specific undiagnosed multi-symptom condition that's pretty unique to Gulf War veterans. Dr. Conboy agreed with Dr. Steele but expressed her opinion that it would be difficult to identify a clean population among individuals who have a disease that isn't well understood.

Dr. Golomb then suggested that Dr. Conboy use Dr. Steele's exclusion criteria from her Kansas study of Gulf War veterans. Dr. Steele remarked that it would not be that much harder to find people who meet her criteria, and that by limiting the study population in that way it would make the study results much easier to interpret. Dr. Conboy expressed enthusiasm for using that approach in her current study, but also stated that she was already having trouble recruiting veterans. Dr. Steele then confirmed with Dr. Conboy that the specific treatments would be designed around TCM diagnostic measures, and that these individualized diagnoses would be recorded as part of the study. Dr. Steele said that she liked Dr. Conboy's idea of assessing whether outcomes vary according to deployment exposures. She expressed confidence that Dr. Conboy could easily conduct an exposure inventory that would be much shorter than many of the other instruments Dr. Conboy was already planning to include. Dr. Conboy replied that she had not been able to find such an instrument that was standard in the field, and Dr. Steele said that she or someone else on the Committee could help Dr. Conboy with that. Dr. Steele said that she had previously looked at some of the modern TCM research in China and she had found a considerable amount of literature on what was termed neurasthenia, which she explained was a cluster of the three groups of symptom types identified as being present in ill Gulf War veterans. She then asked if Dr. Conboy had considered any of those protocols in her study design. Dr. Conboy replied that neurasthenia was included in the practitioner training manual, and that it was very similar to Bi syndrome, which was also recognized by TCM in ill Gulf War veterans and addressed in the training manual.

Dr. Sullivan asked whether the use of needle acupuncture vs. electroacupuncture would be recorded as part of the study. Dr. Conboy said that the type of acupuncture being used on each patient would be tracked. Dr. Sullivan then asked Dr. Conboy to discuss the blood testing in a bit

greater detail. Dr. Conboy replied that the blood would be collected from participants in each group at 4 measurement collection time points (at baseline, after 2 months of treatment or waitlist, and at 2-month intervals from that point on). She added that she was not the expert on what exact biomarkers were being tested, but that she knew that inflammation and immune function would be assessed. Dr. Sullivan then asked, in terms of acupuncture mechanism, if Dr. Conboy could comment on the idea that acupuncture needles might release ATP and thereby cause signaling that reduces pain (i.e. purinergic signaling). Dr. Conboy replied that that was not her bailiwick.

Dr. Sullivan then asked what treatment recommendations Dr. Conboy would make if she found acupuncture to be helpful in some of the veterans, and whether she would expect that acupuncture treatments would need to continue in order for symptom relief to be sustained. Dr. Conboy replied that she had asked a number of practitioners that question and had received varied answers. She said some practitioners thought a level of cure could be reached such that frequency of treatment could be reduced. Dr. Conboy added that, with regard to her study, she did not think that acupuncture treatments could be recommended beyond 6 months. Dr. Sullivan explained that she asked this question because she had heard that military army surgeons were currently using ear acupuncture for battlefield treatments, and that some of these practitioners had recommended such an approach to long-term treatment if acupuncture were found to help Gulf War veterans. Dr. Sullivan then asked Dr. Conboy to reflect on the efficacy of this type of relatively infrequent acupuncture treatment. Dr. Conboy replied that if acupuncture were found to be helpful there were various types of self-treatments that could be administered at home by the veterans themselves, including the small press-balls and moxibustion which she had mentioned in her presentation.

With regard to patient selection criteria, Dr. Sullivan agreed that appropriate exclusionary criteria should be used, but said that she would also be hesitant to excluded too many people because it would be helpful to know whether acupuncture and TCM treatments were effective at relieving multiple symptoms that afflict Gulf War veterans (including those that may fall outside of the strict case definition).

Dr. Steele then asked Dr. Buchwald whether her patients with fibromyalgia who feel they have benefitted from acupuncture treatment have to continue that treatment indefinitely in order to experience continued relief. Dr. Buchwald replied that the answer is really unknown. She also stated that the randomized trials thus far are divided over whether acupuncture helps chronic pain (whereas it does appear to help acute pain more consistently). Dr. Buchwald expressed her belief that the variation was probably due to differences in control groups, and said that she had conducted an acupuncture study in patients with fibromyalgia that were treated twice a week for 12 weeks. She said that no effect was detected at the 6-month follow-up, though other studies had found prolonged beneficial effects at long-term follow-up. Dr. Buchwald said that she offers acupuncture at her clinic and that people who feel like it helps often continue treatment for years, and that acupuncturists typically suggest maintenance treatments, but that the evidence that she was aware of was pretty anecdotal.

Dr. Golomb then commented that at her local VA she can get permission to refer patients outside for chiropractic care for low back pain but that there is a finite window for treatment that would

not allow for chronic treatment of disease outside of the VA system. Dr. Conboy remarked that there are also electrical stimulation devices that can be used in the home by the patients themselves. Dr. Marc Goldstein, the physician who serves as the Medical Monitor for Dr. Conboy's study and runs a pain clinic for several hours each week, stated that he has trained veterans to use devices at home to deliver electric stimulation to specific acupuncture points. He also noted that there are some (fairly expensive) European devices that can be worn on the patient's ear, where they deliver a 1Hz electrical stimulation for 3 days to treat certain types of pain. Dr. Goldstein added that these devices have FDA approval and are currently being looked at in pilot studies in the US. He then remarked that the in-ear acupuncture Dr. Sullivan was asking about (which is called battlefield acupuncture and was developed by Dr. Richard Niemtzow) needed to be more rigorously studied. He said that the needles used in that approach were placed in very specific locations in the ear and meant to be left in for up to a week. Dr. Goldstein said that he thought some veterans might be capable of learning how to use these on their own, but that he did not feel comfortable recommending their use in at-home self-treatment.

Dr. Steele then commented that although some members of the Committee may be unfamiliar with clinical trials such as Dr. Conboy's study which use specific treatments that differ for each participant, she could see that the approach and study design being used by Dr. Conboy was in accordance with the methodologies recommended by the National Institutes of Health (NIH) for the scientific study of unconventional treatments. Dr. Steele explained that the NIH has for many years said that complex treatments could be studied as a "black box" or Gestalt where the study question is not whether one compound affects the outcome, but rather does the treatment approach as a whole result in good measurable outcomes. As such, Dr. Steele expressed her belief that Dr. Conboy's study was a good first step. Dr. Golomb then added that even though scientists commonly think of giving one drug of one dose as giving the same treatment to everybody that is far from the case because people have enormous differences in assimilation, processing, metabolism, etc.

MAJ Nichols then said that she would like to see the acupuncture study model expanded to reach veterans outside the Massachusetts area. She suggested contacting and attempting to recruit the participants from the prior Boston University imaging studies since, from her understanding, these participants had fairly consistent exposures in the war. Dr. Sullivan said that she thought MAJ Nichols had a good point, and suggested that a good way to disseminate the information regarding Dr. Conboy's study would be to have her create a website with information about her study which Dr. Sullivan, MAJ Nichols and others could refer interested veterans to.

Dr. White then commented that the Committee frequently receives calls and emails from veterans interested in participating in studies and that these individuals are referred to the proper channels. She remarked that unfortunately she could not simply contact veterans who had participated in her previous studies since she would have to receive Institutional Review Board (IRB) approval in order to do so.

Chairman Binns then remarked that the Committee exists in order to further discussion of and progression towards treatments. He expressed his appreciation to Dr. Conboy for coming to speak to the Committee about her research, and for putting thought into trying to accommodate

an unconventional background in terms of researching the ways in which TCM would interpret Gulf War Illness. Chairman Binns then called for a brief break.

Update of VA Gulf War Research

Dr. William Goldberg, VA Office of Research and Development

Dr. Goldberg began his update by commenting that all Committee members should have recently received copies of the 3 Gulf War-related Requests For Applications (RFAs) that the VA had issued in February 2010. He remarked that the proposals received by the VA in response to this round of these RFAs would soon be reviewed. Dr. Goldberg explained that the RFAs were being re-circulated to the Committee at the current meeting because they were due to be revised and reissued in January 2011. Dr. Goldberg stated that the RFAs needed to be reissued due to changes the VA was making to the proposal format. He said that the new format would be more like that used by the NIH, in that it will require applicants to include a separate, one-page, specific aims section. Since this change would have to be made to the text of the RFAs before reposting them to the VA website, Dr. Goldberg wanted to present the Committee with the opportunity to make suggestions regarding any content of the RFAs (as he had to the Gulf War Steering Committee). He noted that the version recently distributed to the Committee included the language changes previously recommended by Mr. Hardie and other members of the Committee.

Dr. Steele asked how many proposals had been received in the previous rounds of RFAs. Dr. Goldberg replied that 9 proposals had been received in the most recent round, and that these were awaiting review. He stated that the previous round had elicited 13 proposals, 3 of which had been funded (including Dr. Cook's ongoing research which was presented the day before).

Dr. Sullivan asked for clarification regarding what would be done with any comments the Committee made at the current meeting. Dr. Goldberg replied that the Committee could request additions or omissions to the text of the RFAs so that they could be edited prior to being re-issued.

Dr. Steele then asked why Dr. Goldberg thought he would receive more proposals in the next round of the RFAs. Dr. Goldberg said that question had been raised at the meeting with the Gulf War Steering Committee (herein after referred to as the Steering Committee) as well, and that Dr. O'Callaghan, Dr. White and Mr. Hardie (as members of the Steering Committee) had weighed in on that discussion. He explained that in addition to revised versions of these 3 RFAs, the VA would be issuing 3 companion RFAs specifically for pilot projects that would hopefully draw in new researchers with bright ideas who may lack the preliminary data required to successfully apply for the existing RFAs.

Dr. Steele remarked that it appeared to her that most of the large ongoing Gulf War research projects had not come in via RFAs but rather had been requested specifically by the Office of Research and Development (ORD). Dr. Goldberg agreed. Dr. Steele then asked if other types of project development had been considered in order to solicit specific kinds of studies that are needed. Dr. Goldberg replied that the Cooperative Study Proposal which Nancy Klimas helped develop at the request of ORD (CSP585) was going to focus on creating a cohort, with the first

step being a feasibility project to ensure that the plans for recruiting veterans, gathering samples, test questionnaires, etc. were all going to work. He said that once the cohort was established there would probably be a process that would allow the cohort to become available to a large number of projects. Dr. Goldberg expressed hope that, once recruited, this cohort could be used as a resource for a significantly larger number of studies and would hopefully remove the impediment to access and finding subjects. Dr. Steele asked if there was a timeline by which Dr. Goldberg hoped to have established the cohort. Dr. Goldberg replied that he did not, though he believed that the feasibility project would move forward quickly as a service-directed project prior to final proposal review. He explained that the full proposal for constructing the proposal was still being worked on, but should be done within the coming year. Dr. Steele asked how the intentions for that and the RFAs fit into the idea that the Steering Committee was established in order to develop a comprehensive plan from which these projects would flow. Dr. Goldberg asked Dr. White to weigh in on where the Steering Committee stands.

Dr. White explained that the Steering Committee had held 2 meetings thus far. The first involved a conference call during the summer of 2010 during which members went over the similarities and differences between the 2008 RAC Report and the 2010 IOM Report (Volume 8). The second Steering Committee meeting was held in September with Dr. Joel Kupersmith, Dr. Goldberg and others at VA Central Offices (VACO) to talk about the CSP585. Dr. White explained that at that meeting the members of the Steering Committee were disappointed not to have a protocol to review. They were told the reason for this was that the study was being remorphed because the specific aims of the study did not align sufficiently with objectives associated with Gulf War Illness. As such, Dr. White explained that the push was being directed at having the Epidemiologic Research and Information Center (ERIC) develop a cohort of at least 30,000 people. Dr. White stated that the Steering Committee was asked to approve the idea of going ahead with the cohort formation so that the suite of studies that were going to be carried out with the larger funding could develop off of the cohort. Dr. White recalled that the Committee approved going ahead with the cohort but it expressed that it wanted to be able to review the protocol for selection criteria, exclusion criteria, what kinds of survey questions would be asked, and what kind of samples would be taken. She remarked that she had not heard back from VACO, and that she did not feel that the Steering Committee had been given the opportunity to serve as a true steering committee. Dr. White clarified that the Steering Committee has not had a chance to weigh in on what a unified, centralized, well-organized Gulf War Illness research program would look like within the VA. She added that the Steering Committee had not been given the opportunity to say which questions its members think need to be answered, how they could be answered or what kinds of structures could be used to answer those questions. Dr. White said that so far the Steering Committee had been reactive rather than proactive, and that this was too bad because the group was comprised of experts (though not all of them were very familiar with Gulf War Illness). She felt that the Steering Committee had engaged in a good discussion about the cohort in which important issues were addressed, such as whether to include Genome-Wide Associations (GWAs), and whether 30,000 people was a large enough sample. Dr. White expressed her confidence that the Steering Committee could provide the expertise needed in order for the VA to go forward with an integrated, well thought out Gulf War Illness research plan, but said she doesn't feel that the Steering Committee was being used to its fullest potential. She said that more work needed to be done to make the Steering Committee a more active group. Dr. Goldberg added that the Steering Committee had also asked

about overlap with other programs such as the Congressionally Directed Medical Research Programs (CDMRP).

Dr. O'Callaghan commented that he would characterize the most recent meeting as an information-gathering event, rather than a proactive or reactive meeting. He remarked that many of the individuals on the Steering Committee had to be brought up to speed somewhat regarding Gulf War Illness, and that Dr. White had provided a good overview which contextualized the content of the meeting. Dr. O'Callaghan then brought up a criticism he had at that meeting regarding VA investigators garnering close to 1/3 of the CDMRP funding. He stated that these investigators had been funded by the CDMRP and some other mechanisms but had not yet engaged in the RFA process. Dr. Goldberg responded that a number of individuals who had VA funding also had projects funded through CDMRP. He added that the Steering Committee had requested that someone from the CDMRP come to their next meeting to demonstrate how an integrated non-overlapping program could be developed from what exists.

In light of the fact that the Steering Committee was not presented with an integrated research plan to approve or review, Dr. Steele asked if any Gulf War strategic research plan existed yet. Dr. Goldberg replied that this was what he hoped the Steering Committee would help develop. He added that the Steering Committee had been shown the RFAs, which he explained couldn't be eliminated because the VA needs a mechanism for merit review level projects that come in. Dr. Steele said she was not suggesting that the RFAs should be gotten rid of, rather that the content and types of studies that are also solicited should be based on what the Steering Committee decides are the main objectives. Dr. Goldberg replied that the RFAs were provided to the Steering Committee so that they could make intelligent decisions about what content would be important in the Gulf War research program. Dr. Goldberg then acknowledged the arrival of Mr. Hardie and asked if he would like to reflect on the Steering Committee meeting.

Mr. Hardie first thanked Dr. White for helping to put together the Pike Conference to Examine Care and Advocacy for America's Veterans, then remarked on the health troubles he has experienced in the past several weeks (including spells of dizziness, one of which caused a serious fall resulting in a fractured sacrum). He then thanked Dr. Goldberg for aligning the language of the RFAs with that used by the IOM and CDMRP, as well as for changing the RFAs according to his recommendations, such that no proposal would be funded that focused on psychological stress. Mr. Hardie then remarked that he continued to hear researchers call for the creation of consortiums to solve the problem of Gulf War Illness, and to do so may involve the need for Congressional language, beyond the VA's RFAs. Mr. Hardie also remarked that he would love to see VA do more outreach with Gulf War veterans. He stated that he felt VA was moving in the right direction, but that if the agency was truly serious about changing its culture, it needs to put in a request for funding at the level that is solving veterans' problems of Post-Traumatic Stress Disorder (PTSD), Traumatic Brain Injury (TBI) and prosthetics.

Chairman Binns then addressed the issue of how to devise a comprehensive Gulf War research plan. He remarked that he had participated in a call with Dr. White, Dr. Kupersmith and some others regarding the new research director position that was announced by Mr. Gingrich at his testimony in July. Chairman Binns stated that in that conversation Dr. Petzel made it clear that there would be a comprehensive plan, the creation of which would be led by whoever takes over

the leadership of Gulf War illness research. That said, Chairman Binns stated that there was currently what he hoped would be a temporary confusion between the position as posted (which appeared to be for a deployment health research director) versus the position for a research director of Gulf War and environmental exposures (as it was understood by the Committee when announced). He expressed hope that the confusion would be resolved and that the person who becomes the leader of that Gulf War and related exposures research effort would be the one who would lead the creation of a comprehensive plan. He then remarked that just as the Committee (which meets 3 times a year) is not equipped to create the plan, neither is the Steering Committee well equipped to actually create the plan. Rather, Chairman Binns voiced the need for a centralized seat of responsibility for that role coming from VA, and said that he can understand why the Steering Committee had not yet been tasked with creating the comprehensive plan because their has been no centralized work on this to date.

Dr. Goldberg explained that there had been 2 job announcements, 1 for a PhD and another for an MD, since VA did not know who might apply for the position. He added that the Committee members would find both job announcements in their binders of materials. Dr. Goldberg remarked that the individual being sought would most likely be a toxicologist that would deal with exposure-related issues, including those associated with Gulf War Illness. He added that ORD currently deals with other exposure-related issues, including burn pits, and would likely soon be dealing with Camp Lejeune issues, sodium dichromate issues, and other areas that would require the expertise of a new staff member. Dr. Goldberg remarked that he believed the creation of the new position would strengthen the place of Gulf War Illness within ORD far above where it currently stood. He also remarked that the job description was not written by ORD, and that it had not intentionally been written to differ from the position that Mr. Gingrich had outlined. Dr. Goldberg explained that the individual to be hired would have to take on more than just Gulf War Illness-related exposures. He added that ORD must serve all of the veteran populations, while also responding to the Secretary's office and issues that come down from Capitol Hill.

Chairman Binns replied that he felt reassured by that information but that the problem of recruiting an appropriate individual for the job remained, since applications would be submitted based on the broad existing description. He said that because the job title was for a director of "deployment health" he had assumed that the position would involve managing all deployment health issues, and as such he found the description to be a potential deterrent for qualified individuals with expertise in Gulf War and exposure health issues. Dr. Goldberg replied that if ORD didn't receive applications from sufficient candidates to fulfill the roles laid out by Dr. O'Leary and Dr. Kupersmith, the position would have to be re-announced. Chairman Binns then expressed doubt that a desired candidate would apply based on the current job description. Dr. Goldberg replied that the first applicant had been interviewed, and that individual was a toxicologist.

Chairman Binns recollected that the need for a toxicologist arose when the job had been envisioned as a lower, portfolio-management position. Chairman Binns said that was not what he had in mind when he proposed the idea, nor did he think it was what Mr. Gingrich had in mind when he discussed the position. He said that he was happy to hear that the core intent remained the same, but that work needed to be done in order to achieve those aims and find an appropriate individual for the position.

Mr. Hardie then remarked that Gulf War veterans had been calling for treatment-focused research for a long time, and that there had been a growing call among Gulf War veterans testifying before Congress over the past number of years for a dedicated Gulf War Illness office. Mr. Hardie said that often government hiring processes involve encouraging people to apply from a known candidate to apply, and that he did not know whether that was happening in this case. He remarked that regardless of whether that was taking place, solving Gulf War Illness would not happen with a staff person who had to divide their attention between many different non-Gulf War exposures as well. Mr. Hardie stated that elected and appointed officials still needed to be told that Gulf War health issues needed to be solved, and that in order to do so significantly more resources would be necessary. He then mentioned research that Mr. Paul Sullivan had been conducting with Ms. Linda Bilmes calculating the cost of war, which has estimated that war was costing $1 million per disabled veteran for their health care and compensation. Mr. Hardie expressed his belief that focusing on treatments to improve the health and lives of veterans could save VA a lot of money. He said that the new position was a piece of what he and other Gulf War veterans were looking for, and that was better than nothing, but that it was not the whole nor the direction of what Gulf War veterans were looking for. Mr. Hardie asked Dr. Goldberg to carry that message back to his directors, and Dr. Goldberg replied that he would.

Chairman Binns then asked if anyone had comments on the RFAs. Dr. Sullivan reiterated Mr. Hardie's remark that many of the Committee's previous recommendations had been put into the RFAs. Dr. Steele then took the opportunity to underscore that point, noting that the RFAs had come a long way from where they started, and that they are generally more than acceptable. She then asked if the Committee members would be given any time to read over the RFAs before making any additional recommendations. Dr. Goldberg replied that if there were no comments that needed to be discussed then any comments from individual Committee members could be dealt with on the basis of personal expertise, as had been done in the past. Chairman Binns then asked if all of the Committee members were comfortable with the decision not to make any Committee-level recommendations on the RFA. The Committee was in agreement.

Chairman Binns then asked if the same process would be implemented for the Committee to make recommendations and its members to submit comments regarding the pilot RFAs. Dr. Goldberg explained that the content of those RFAs would include the same background text and would essentially only differ in that they would be explicit about the structure for pilot projects' duration, dollar amounts, etc. He said that he thought the Steering Committee agreed that those RFAs were likely to bring in new researchers who would not have been in a position to apply to the existing RFAs. Dr. Goldberg stated that he envisioned the pilot projects continuing on into larger collaborative research studies among a growing cadre of Gulf War Illness investigators.

Dr. Buchwald asked if the format would remain in the old NIH 25-page format. Dr. Goldberg replied that ORD was still running a 25-page research plan but that in February ORD plans to modify that format to a separate 1-page specific aims component of the research plan and the rest of the research plan would probably go down to 24 pages. He expressed his belief that this would help investigators focus their research aims while also making the review process easier and more effective for the reviewers. Dr. Goldberg remarked that he did not think ORD would decide

to limit the proposals to 12 pages like NIH, but that 25 pages may be deemed too long. Dr. Buchwald encouraged Dr. Goldberg to expedite that process because, from her experience, an investigator is much more likely to submit a 13-page proposal than a 25-page proposal. She then explained that the new NIH format incorporated a 1-page specific aims section and 12 pages for the rest of the proposal. Dr. Buchwald said that she believed this new format results in better proposals since investigators have to condense their proposals into less space. She added that the new NIH format also de-emphasized the amount of detail needed in the methodologies section and added new sections on innovation and significance. Dr. Goldberg replied that several VA investigators had already submitted 12-page proposals that were rejected by the reviewers for lack of detail and justification. Chairman Binns asked if perhaps that simply indicated that those proposals were not good. Dr. Goldberg replied that it was possible, though the applicants were senior researchers who had been successful at NIH. He clarified that the point he was trying to make was that reducing the number of pages to 12 would not necessarily improve the quality of the applications. Dr. Goldberg then acknowledged that there was growing agreement at ORD that 25 pages was probably too long, and the appropriate length still had to be determined. He added that the process of changing the length and format would take time. Dr. Buchwald remarked that, in her opinion, the more ORD makes its format different from that of NIH the less successful ORD would be in getting people to submit applications. She advised ORD to therefore make their format as closely aligned with NIH as possible.

Dr. Meggs remarked that most private foundations he has applied to for funding use a format identical to the NIH format, and that he has found that to be very helpful.

Chairman Binns remarked that it was time to move on, and then asked Dr. Goldberg if he had any other issues to discuss. Dr. Goldberg replied that he did not.

Chairman Binns then asked if he was correct that the VA's proposed 20-year follow-up study of a national cohort of Gulf War veterans was not an ORD project. Dr. Goldberg confirmed that the survey-based study was not an ORD survey but was being coordinated under the Environmental Epidemiology Service (EES), which is a division of the Office of Public Health and Environmental Hazards at the Veterans Health Administration (VHA).

Dr. Steele then asked about the list of the funded studies that Dr. Goldberg had printed off for the Committee members (see Appendix B – Document 1). She asked for clarification on why studies that end dates in 2009 were listed as receiving 2010 funding. Dr. Goldberg replied that some of the studies may have received extensions, while others may have had errors printed in their end dates (especially since projects that start later than October 1st extend into the next fiscal year). He said that he had caught some of those but may not have caught all that were included in the list.

Dr. Sullivan commented that she had noticed the 3 recently-funded Gulf War studies were all treatment related. Dr. Goldberg interjected that they were not on the list because no money flowed to them in fiscal year 2010 because most were still getting through IRB approval. He said that those 3 projects were technically 2011 projects since they couldn't start until after October 1, 2010. Dr. Sullivan then thanked Dr. Goldberg for providing the Committee with those 3 studies' abstracts, as those were more informative than just the study titles (see Appendix B – Document

2). She also agreed with Mr. Hardie's call for consortium-style research, but she also acknowledged the value of small treatment trials conducted by individual researchers who want to test their ideas on a small scale before conducting large studies.

Dr. Goldberg then explained that the other reason he had distributed the ongoing research abstracts was to demonstrate that although the principal investigator must be a VA employee, other senior/key personnel who were not affiliated with the VA could be involved in the research.

Mr. Hardie then said that he was very pleased to see the Gulf War Veterans' Illnesses Task Force Report come out, but that he was displeased not to have found out about the report's release from the VA, even though he currently served as a member of the Committee, the Gulf War Steering Committee and CDMRP. Mr. Hardie then requested that hard copies of these reports be mailed to everyone on all 3 of those committees, as well as past members of the Gulf War Advisory Committee which had been discontinued. Dr. Goldberg replied that in many ways Mr. Hardie was correct, and that it even took him a while to find the electronic version of the report on the VA website. Dr. Goldberg then said that he would provide the link so that anyone going to the Committee's website could link directly to the report from there. He added that EES has a website on Gulf War issues, and that it was not always easy to find it or the Committee's website using a search engine query. Dr. Goldberg said that this issue had come up at the Steering Committee meeting and that the suggestion was made to be sure that these websites were linking to each other. Mr. Hardie added that outreach to Gulf War veterans could be improved, specifically by providing hard copies of these reports at Committee meetings.

Dr. Goldberg then apologized that ORD's 2008 and 2009 annual reports to Congress were currently at the printer. He added that it took a very long time for the report to get through concurrence at VA. He stated that there would be hard copies of those reports available at the next meeting.

Chairman Binns then thanked Dr. Goldberg and called for a quick break.

Committee Discussion: 2011 Planning

Mr. Jim Binns, Chairman, Research Advisory Committee on Gulf War Veterans' Illnesses
Dr. Kimberly Sullivan, Research Advisory Committee on Gulf War Veterans' Illnesses

Chairman Binns opened the discussion session by asking Dr. Sullivan to provide an overview of the issues needing to be addressed by the Committee (see Appendix A - Presentation 14). Dr. Sullivan began the discussion by outlining several recommendations regarding the VA's proposed "Follow-up Study of a National Cohort of Gulf War and Gulf Era Veterans," after which she asked for comments from the Committee members.

Dr. Meggs remarked that if the survey was going to ask about alternative therapies it should also ask about conventional therapies, and whether the veterans felt these treatments helped them. He added that many veterans report developing intolerances to foods, chemical odors, pollen, alcohol as well as to bright lights, loud noises, and even to touch. Dr. Meggs suggested that the

survey should ask about these hypersensitivities, as well as any related avoidance activities that the veterans may have found helpful.

Dr. Buchwald then asked for clarification on who the survey would be distributed to. Dr. Sullivan replied that, from her understanding, it would be circulated to 18,000 veterans, 10,000 of which would be Gulf War veterans. She asked Dr. Goldberg to clarify whether these individuals would necessarily be patients. Dr. Goldberg replied that the veterans being surveyed were a "permanent cohort" recruited by Dr. Han Kang shortly after the end of the Gulf War, and that this survey would be the 20-year follow-up (making it the third or fourth round of surveys which this cohort had received). Dr. Buchwald asked what the expected response rate was, based on the previous surveys. Dr. Goldberg replied that he believed the response rate had dropped to between 15-18 percent. Dr. Buchwald remarked that she felt the response rate needed to be balanced with the intensity of the questions, since there is some relationship (though not a linear one) between willingness to participate in a survey and the length of that survey. Dr. Buchwald then commented on the existence of a consortium of 6 sites funded by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) to look at chronic unexplained pelvic pain and its comorbidities. She explained that the self-reported screening criteria for the overlapping disorders have been carefully developed and pilot-tested in a web-based format which could be very useful in the Gulf War survey. Dr. Buchwald added that the project is known as the Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) and that John Kusek and Chris Mullins are the program officers at NIDDK.

Mr. Hardie expressed his support for Dr. Sullivan's recommendations and made a few comments regarding additions he would like to see in the survey. For survey recipients who have died, Mr. Hardie requested that there be a component for a family member to fill out cause of death. Mr. Hardie would also like to see questions added to the survey regarding veterans' experiences with repeated or chronic infections of any kind, including sinusitis. Mr. Hardie stated that VA claims representatives have told him that Gulf War veterans report chronic sinus problems more than veterans of other wars. He said that the survey should include additional respiratory diseases, including bronchiolitis. Mr. Hardie also thought it would be important to ask about specific dermatologic conditions and diagnoses related to dyspepsia. He added that he and other Gulf War veterans suffered from gastroesophageal reflux disease (GERD). Mr. Hardie also felt that the survey should ask about previous surgeries and hospitalizations veterans had undergone.

Dr. Steele stated that she concurred with all comments made by the Committee members thus far, and expressed her strong reservations about the survey, noting that she had a long background in survey research and questionnaire development. She remarked that the current survey was inconsistent with the previous surveys in the level of detail and way in which questions were written. For example, she said that the 1995 survey questioned 48 symptoms in a systematic way but the current questionnaire asked about only 8 symptoms in that way. Dr. Steele added that the current survey did not involve systematic collection of medical information or health care utilization that would provide a snapshot of Gulf War veterans' health. She also remarked that the survey did not get at the answers to pressing questions that Congress and others have asked the VA to look at, such as Multiple Sclerosis (MS), different types of cancers, and health outcomes in family members. Dr. Steele stated that there were so many details that need to be addressed in the survey that she would advise the Committee to recommend that the

survey be put on hold until the new Director of Gulf War Research is found and a research plan has been devised which can integrate the survey with the goals of the larger research plan, to ensure that the survey can help achieve those goals.

Dr. Buchwald commented that a critical point to underscore is that the data of a longitudinal study is useless unless questions are asked in the same way over time. She said that whoever was developing the survey should focus the current survey on the "big hits" of the original questionnaire, and to then be sure that the questions are asked in the same way as they originally were. Dr. Sullivan remarked that part of the problem was that the study was never envisioned as a longitudinal study, so the questions were not asked in consistent ways with each new iteration of the questionnaire.

Dr. White agreed with Dr. Steele's basic point, and stated that she did not understand how the survey was being coordinated with the rest of the VA Gulf War research effort. She consented that some new questions might need to be asked, and that these could be worded in ways different from the questions that were consistent over time. Dr. White also commented that she thought the Gulf War Steering Committee would be happy to look at the survey.

Chairman Binns remarked that Dr. Han Kang and the DoD funders had previously agreed to postpone the distribution of his second survey when the Committee expressed desire to make comments on it. In addressing the current survey, Chairman Binns stated that individual Committee members could possibly submit comments for review by the Steering Committee. Dr. White responded by stating that the Steering Committee had not been asked to look at the survey, so she did not know who the Steering Committee would pass the comments on to. Dr. Meggs suggested utilizing the mechanism for making comments in the Federal Register, noting that the deadline of submitting written comments online was November 8. Dr. Buchwald stated that she felt the best strategy would be to create and submit a summary statement on behalf of the Committee that captured the Committee's conceptual concerns regarding the need for a review of the survey and coordination with past surveys. Chairman Binns remarked that he saw no time urgency for the release of the survey, since it should flow from a plan that did not exist yet. As such, he suggested that part of the Committee's recommendation should be that the survey be reviewed by the Committee, which was never asked to review it. Dr. Steele then asked Chairman Binns to clarify the nature of the Committee's comments. Chairman Binns stated that he would like the Committee's comments to meet the standard of a Committee recommendation both as an on-site submission and as a recommendation to the Secretary of the VA's office. Chairman Binns asked the Committee if they were in agreement to follow the approach outlined by Dr. Steele and Dr. Buchwald. Mr. Hardie said that he concurred with their proposals. Chairman Binns then announced that a brief recommendation would be drafted and circulated to all of the Committee members stating that the survey was not ready for prime time. Dr. Buchwald then asked if anyone could clarify who put the survey together. Dr. Goldberg responded that it was not being done as a project through ORD but rather as a function of the EES, and that the survey would be funded by VHA. He explained that they were in a whole other chain of command that ORD does not have authority over. Dr. Buchwald remarked that the problem was that the survey would still be used as a research tool, yielding erroneous conclusions. Chairman Binns concurred that the survey directly related to research, and explained that the Committee was not simply

asking ORD to coordinate with itself but rather asking VA to look at the issues the Committee raised about the survey.

Dr. Sullivan then proceeded to address the next topic for discussion: the Final Gulf War Veterans' Illnesses Task Force Report (hereinafter referred to as the Task Force Report). She explained that the Committee had not made formal recommendations regarding the Task Force Report draft because the comment period had fallen during a period when the Committee was not meeting. As such, a subgroup of Committee members had put together and submitted a series of comments on the draft Task Force Report. Dr. Sullivan then provided an overview of the degree to which comments made by the subgroup of the Committee were incorporated into the final Task Force Report (see Appendix A – Presentation 14). She then asked if any of the Committee members had specific comments on issues or concerns with the final Task Force Report.

Mr. Hardie expressed his concern that the VA had not involved stakeholders, a problem which he saw as a continuing issue within the VA. He said that, to his knowledge, there were no outside stakeholders involved in the writing of the Task Force Report. Mr. Hardie remarked that the VA had to listen to people [veterans and the Committee] in order to be serious about changing the culture at VA. He expressed his frustration that the scientific experts on the Committee were not consulted in the process of writing the Task Force Report. Mr. Hardie also said that he found it unacceptable that the Committee only found out about the survey from a veteran who noticed its announcement in the Federal Register.

For the sake of time, Dr. Sullivan passed over discussing the Director of Deployment Research position since it had come up in an earlier discussion at the meeting. She then briefly summarized the annual operations plan for the Committee's upcoming year (see Appendix A – Presentation 14). In her presentation, Dr. Sullivan spoke about the proposed themes for future invited speakers and VA briefings. During this discussion she asked Dr. Goldberg if the clinician training manuals had been completed. Dr. Goldberg did not know if the new training materials had been implemented or not, adding that the EES was also overseeing that process. Dr. Sullivan then expressed her desire to have the Committee updated on the environmental exposure trainings that were supposed to have happened over the summer of 2010. Dr. Goldberg said that he knew of at least 2 exposure trainings that had taken place, and that Dr. Cassano would be the person to ask about both of the issues she had just raised. The final government speaker topic that Dr. Sullivan suggested was to invite Secretary Shinseki to address the Committee on February 28, in recognition of the 20th anniversary of the cease-fire ending the ground war. Dr. Goldberg cautioned that the Secretary's schedule was extremely busy, and encouraged the Committee to begin that request process ass soon as possible. Dr. Sullivan then asked if any of the Committee members had additional suggestions for speaker topics or anything that wasn't covered.

Dr. Buchwald said that she would be interested in a presentation on systems biology integrating perspectives from the molecular level up to clinical situations. She said that she would also value hearing about Gulf War Illness as experienced by service men and women from different countries that participated in the Gulf War.

Mr. Hardie remarked that he would like to hear from some Gulf War veterans that perhaps had not been at previous meetings. He suggested that 5-6 veterans could each be invited to present for 5 minutes with pictures and/or recollections from the war. Mr. Hardie also said that he would like to be involved inviting the press, but that the goal would be to remember and reflect on the service of Gulf War veterans with stories that would be new to the Committee.

Dr. Buchwald then remarked on the importance of personal narratives, noting that 25 years ago when she began studying chronic fatigue she had done a grand rounds wherein the most powerful part was bringing in a faculty member at the university to speak about her experience having the disease. Dr. Buchwald suggested asking Gulf War veterans to speak about anything they may have found to help their condition. Mr. Hardie approved of this suggestion.

Chairman Binns then asked the Committee members to continue to think about the process that they would like to see unfold. He specifically requested that they envision what should happen after the VA Gulf War Research Plan was in place, encouraging people to think outside the box in order to bolster the quality of future meetings.

Dr. Sullivan then outlined the proposed meeting dates for 2011, in addition to other details regarding meeting format, literature review, and the planned 2009-2010 scientific summary report (see Appendix A – Presentation 14).

Chairman Binns then called for public comments.

Public Comments

SSG Bryan asked if there was an epidemiologist available on the Committee to inform the veterans about how the exposures happened, particularly to oil well fire smoke. He stated that the doctors at the VA in Boston and Texas don't know much about oil well fires or DU. SSG Bryan expressed his desire to see epidemiological research of the causes of Gulf War Illness, noting that it would play a key role in Compensation and Pension for veterans. Dr. Steele replied that over half of the Committee's 2008 Report was dedicated to an extensive review of the numerous epidemiology studies looking into the causes of Gulf War Illness.

MAJ Nichols agreed wholeheartedly on the Committee's recommendation to hold off the release of the survey until it was corrected. She also asked the Committee to approve the inclusions of survey questions on coagulation, inflammation, surgical history (disc surgeries in particular), vision, hearing and dental problems, as well as cardiovascular problems (especially strokes, pulmonary embolisms and heart surgery). MAJ Nichols then remarked that veterans' spouses could often provide insight into the neurocognitive symptoms that Gulf War veterans were suffering from. She also requested that the survey ask whether veterans are receiving aid and attendants at home, because many veterans are in need of those services. MAJ Nichols then commented on the break-down of information flow regarding the survey. She suggested that the home page of the VA website list all Federal Register notices that it submits.

Chairman Binns thanked everyone for their contributions and adjourned the meeting at 1:25pm.

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