Research Advisory Committee on Gulf War Veterans' Illnesses

March 1-2, 2010, Committee Meeting Minutes

Department of Veterans' Affairs
Washington, DC

DEPARTMENT of VETERANS AFFAIRS

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

/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
Floyd Bloom
Dedra Buchwald
Beatrice Golomb*
Joel Graves
Anthony Hardie
Marguerite Knox
William Meggs
James O'Callaghan
Steve Smithson
Adam Such
Lea Steele

Consultant to the Committee
Jack Melling

Committee Staff
Kimberly Sullivan
Sadie Richards

Designated Federal Officer
Bill Goldberg

Other Members of the VACO
John Gingrich, VA Chief of Staff
Joel Kupersmith, VA Chief Research and Development Officer
Lois Mittelstaedt, Chief of Staff, VBA Office of the Under Secretary for Benefits

Guest Speakers
Peter Baas
Douglas Fields
Robert Haley
Nancy Klimas
Bjorn Knudtzen
Gudrun Lange
Vidar Lehmann
Mariana Morris
Linda Watkins

* participated by phone

Abbreviations

ALS – Amyotrophic Lateral Sclerosis

CAM – Complementary and Alternative Medicine

CB2 – Cannabinoid

CBT – Cognitive Behavioral Therapy

CDC – Centers for Disease Control and Prevention

CDMRP – Congressionally Directed Medical Research Programs

CFS – Chronic Fatigue System

CNS – Central Nervous System

CSP – Cooperative Studies Program

CT – Computer Tomography scan

DoD – Department of Defense

DTI – Diffusion Tensor Imaging

fMRI – functional Magnetic Resonance Imaging

GW – Gulf War

GWVIS – Gulf War Veterans Information System

MRS – Magnetic Resonance Spectroscopy

MS – Multiple Sclerosis

NAA – N-acetyl-aspartate

NIH – National Institutes of Health

OEF/OIF – Operation Enduring Freedom/Operation Iraqi Freedom

OP – Organophosphate

ORD – Office of Research and Development

PB – Pyridostigmine Bromide

PDICI – Post Deployment Integrated Care Initiative

PET – Positron Emission Tomography scan

PI – Principal Investigator

PON1 – Human Paraoxonase-1

PTSD – Post Traumatic Stress Disorder

RFA – Request for Application

TBI – Traumatic Brain Injury

THC – Tetrahydrocannabinol

TLR4 – Toll-Like Receptor-4

UTSW – University of Texas Southwestern

VAEES – Veterans Affairs Environmental Epidemiology Service

VBA – Veterans Benefits Administration

VHI – Veterans Health Initiative

VSO – Veterans' Service Organization

WRIISC – War-Related Illness and Injury Center

XMRV – Xenotropic Murine leukemia virus-Related Virus

Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses
March 1-2nd, 2010
Veterans Administration, 810 Vermont Avenue, Room 230, Washington, DC

Agenda
Monday, March 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	**Glia --The other brain**	**Dr. Douglas Fields** **National Institutes of Health (NIH)**
9:30 – 10:30	**Chronic pain and glia**	**Dr. Linda Watkins** **University of Colorado**
10:30 – 10:45	**Break**	
10:45 – 11:30	**Microtubules and neurodegeneration**	**Dr. Peter Baas** **Drexel University**
11:30 – 12:00	**XMRV virus, chronic fatigue and Gulf War illness**	**Dr. Nancy Klimas** **Miami VAMC**
12:00 – 12:30	**Planned survey of the health situation of Norwegian Gulf War veterans**	**Dr. Vidar Lehmann &** **Dr. Bjorn Knudtzen** **Norwegian Armed Forces Medical Services**
12:30 – 1:30	**Lunch**	
1:30 - 2:15	**UTSW neuroimaging studies update**	**Dr. Robert Haley** **University of Texas Southwestern** **VA Dallas Healthcare System**
2:15 – 3:00	**Long-term health effects from sarin exposure**	**Dr. Mariana Morris** **Wright State University**
3:00 – 3:15	**Break**	
3:15 –4:30	**Committee discussion: 2009 annual report**	**Dr. Roberta White and** **Committee discussion**
4:30 – 5:00	**Public comment**	

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

Veterans Administration, 810 Vermont Avenue, Washington, DC

Agenda
Tuesday, March 2, 2010

8:00 – 8:30	**Informal gathering, coffee**	
8:30 – 9:15	**War-Related Illness and Injury Centers (WRIISC) research program update**	**Dr. Gudrun Lange** **DVA NJ Healthcare System**
9:15 – 10:00	**Gulf War Veterans Information System (GWVIS) report and tracking update**	**Ms. Lois Mittelstaedt** **Chief of Staff, VBA Office of the Under Secretary for Benefits**
10:00 – 11:00	**VA Gulf War Task Force**	**Mr. John Gingrich** **Chief of Staff** **Dept. of Veterans Affairs**
11:00 – 11:15	**Break**	
11:15 -11:45	**Advisory Committee on Gulf War Veterans: Final Report recommendations**	**Mr. Steve Smithson** **Res. Adv. Cmte Gulf War Illnesses**
11:45 – 12:45	**New VA Gulf War Research Program**	**Dr. Joel Kupersmith** **Chief Research and Development Officer** **Dr. William Goldberg** **Scientific Program Manager GW research** **Dept. of Veterans Affairs**
12:45- 1:15	**Public Comment**	
1:15	**Adjourn**	

DAY 1

The March 1-2, 2010 meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses (hereinafter referred to as the Committee) was held in Room 230 at the Department of Veterans' Affairs, 810 Vermont Avenue, NW, Washington, D.C.

Welcome, Introductions & Opening Remarks

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

Chairman Binns called the meeting to order at 8:30am. He then outlined several revisions to the agenda before asking Dr. Sullivan to proceed with opening remarks. Dr. Sullivan explained that the day's first speakers would be talking about glial mechanisms involved in chronic pain and neurodegenerative disorders. She then introduced Dr. Douglas Fields.

Glia – The Other Brain

Dr. Douglas Fields, National Institutes of Health (NIH)

Dr. Fields provided an overview of the role that glial cells play in neurological functioning and disease. The vast majority of the cells which make up the brain (85%) are non-neuronal cells known as glia. However, because glia do not communicate like neurons do (via electrical signaling across small gaps known as synapses) they have historically been ignored in the study of the brain. Methodologies developed in recent years have revealed that glia form vast signaling networks between each other and neurons. Dr. Fields showed several videos of his research demonstrating that glia interact by broadcasting signals across gaps greater in distance than neuronal synapses. Although glia do not use electrical signals to communicate, they can use the same neurotransmitters as neurons. Thus glia not only interact with each other but with neurons as well. Dr. Fields remarked that this revelation may help explain aspects of many neurological conditions previously thought to only involve neurons.

Dr. Fields explained that there are several types of glia, including microglia that serve as the brain's immune system. Microglia scavenge and kill infecting organisms in the brain, as well as institute repair of injured tissues. Dr. Fields mentioned that this glial activity has been implicated in chronic pain, which develops after an injury heals. He briefly explained how glia can be involved in opiate addiction, adding that promising new pain management drugs that act on cannabinoid receptors found on glia may be able to alleviate pain without causing unwanted side effects.

Dr. Fields then mentioned two other types of glia called oligodendrocytes and Schwann cells. Oligodendrocytes form insulating myelin sheaths around the axons of neurons, thereby allowing myelinated neurons to send signals 100 times faster than unmyelinated neurons, and Schwann cells myelinate nerves in the peripheral nervous system. Dr. Fields also discussed how glia interact with blood vessels by taking up and recycling spent neurotransmitters from neuronal synapses and by absorbing nutrients (e.g. glucose, lactose) from the blood and delivering it to neurons. He added that glia cells known as

astrocytes are also able to control local blood flow by dilating and constricting capillaries in the presence of certain stimuli. Dr. Fields explained that this action of glia allows for the visualization in functional Magnetic Resonance Imaging (fMRI) techniques, which primarily measure blood flow differences in the brain.

Dr. Fields then commented that most brain cancers (e.g. glioblastomas) involve glia, not neurons. Unlike mature neurons, mature glia continue to divide. Based on this knowledge, new treatment approaches have been developed which target only the cancerous glial cells and do not involve invasive brain surgery. Dr. Fields then remarked that even the mature brain has the ability to form new neurons. Because neurons can't divide they are not the source of new neurons. The source of the new neurons are immature glial cells that are generating other glial cells and new neurons.

Dr. Fields spoke next about how glia are the ultimate reason for permanent paralysis. He remarked that new treatment trials using immature glial cells are currently underway which may hold promise for spinal cord regeneration. Speaking of the need to successfully regenerate synapses in addition to inter-neuronal connections in spinal cord regeneration, Dr. Fields noted that in vitro studies reveal that astrocytes influence where and how many neuronal synapses form.

Dr. Fields also discussed the role that glia may play in Amyotrophic Lateral Sclerosis (ALS), which can be caused by a mutation of an antioxidant protein. He explained that astrocytes around these motor neurons are partly responsible for ALS because they play a role in regulating the release of antioxidants, and when they are damaged ALS can result.

Dr. Fields commented on how glia can be involved in Parkinson's disease, which is caused by the death of cells in a region of the brain known as the substantia nigra. He explained that astrocytes release growth factors which help maintain the neurons of the substantia nigra, but they are also capable of taking up or releasing toxins which can kill cells in the substantia nigra.

Dr. Fields then stated that some diseases, such as multiple sclerosis (MS) are strictly glial diseases affecting myelin directly. HIV-related dementia has a glial component and inflammation. Plaques and disabilities associated with Alzheimer's disease involve and affect glia as well as neurons.

Dr. Fields then spoke about the paradigm shift that he sees happening in the field of neuroscience. In the past, the neuronal doctrine focused on neurons and synapses in the brain as the root of neurological and psychiatric dysfunction. New methods of brain imaging (including Diffusion Tensor Imaging, or DTI) have recently revealed the important role of white matter changes in many cognitive diseases. White matter – the myelinated axons of the brain – makes up about half of the human brain, and is formed by oligodendrocytes (a type of glial cell). Recent research studies have shown that learning is associated with increased myelination in relevant areas of the brain. For example, individuals learning to juggle gained white matter volume in the area of the brain responsible for eye-hand coordination.

Dr. Fields has been studying communication between oligodendrocytes and neurons in vitro. This recent research is not yet published, but sheds light on some of the processes discussed above.

At the completion of Dr. Fields' presentation Dr. Sullivan thanked him and opened the floor to questions.

Dr. Bill Meggs, a member of the Committee, asked Dr. Fields what type of communication occurs between astrocytes and microglia. Dr. Fields replied that these glial cells communicate using chemical means, via neurotransmitters and other signaling molecules.

Mr. Binns asked what mechanisms are involved in causing damage to the glial processes. Dr. Fields replied that many toxic insults result in damage to glia. He stated that those most likely relevant to Gulf War illness would include inflammatory and oxidative molecules released after injury. Dr. Fields also suspects that autoimmune disorders and growth factors (many of which are released by both neurons and glial cells) may be involved.

Dr. Roberta White, the Scientific Director of the Committee, commented that she had been seeing patients with white matter diseases for 30 years, before imaging techniques were able to illuminate white matter lesions. Dr. White remarked on the symptom of fatigue that is common to many ill Gulf War veterans and others with white matter diseases. She asked Dr. Fields if he could comment on how fatigue might relate to glia. He replied that white matter changes were historically dismissed as communication breakdown secondary to neuronal changes, but that recent research has revealed that higher level cognitive functioning also relies on white matter circuitry in the brain.

Dr. Lea Steele, a member of the Committee, asked Dr. Fields to clarify whether white matter diseases necessarily involved suboptimal movement through neurons. Dr. Fields reiterated that brain functions rely on both neuronal and glial activity. He added that the communication is bidirectional, such that damage to neurons can affect glia and vice versa. Dr. Fields also noted that myelination occurs throughout life, and that this process has effects on cognition.

Dr. Sullivan asked if, in the event that an axon is damaged and becomes thinner (e.g. as a result of microtubule damage), the myelin sheath will become thinner to compensate for the reduction in axonal diameter. Dr. Fields replied that this is the case, adding that there is an optimal thickness of the myelin sheath in relation to the thickness of the axon fiber. He also remarked that glial cells control the diameter of the axon, with thinner axons conducting signals more slowly than thicker axons.

Dr. Jim O'Callaghan, a member of the Committee, asked Dr. Fields to comment on the most promising classes of therapeutic interventions targeting glial activation. Dr. Fields replied that some of those involved in pain, spinal cord repair and cancer were most

exciting. He said that many drugs used to treat psychiatric illnesses act on glial cells, so pharmaceutical companies are beginning to explore variants of new and existing medications targeted at glia such as drugs targeting specific cannabinoid receptors.

Dr. Sullivan then introduced Dr. Linda Watkins.

Chronic Pain and Glia

Dr. Linda Watkins, University of Colorado

Dr. Watkins spoke about the communication between the brain and immune system, and how pathological pain may arise from such interactions through the involvement of glial cells (see Appendix A – Presentation 1). Dr. Watkins explained how targeting glia and the substances they release (pro-inflammatory cytokines) could provide new ways of alleviating pain and potentially treating a variety of symptoms of Gulf War Illness. In her presentation, Dr. Watkins discussed several clinically relevant animal model studies which have demonstrated that blocking glial activation by targeting receptors involved in pro-inflammatory cytokine signaling effectively suppresses neuropathic pain, returning the pain threshold to a normal level. Research carried out by Watkins and others also strongly predicts that blocking glial/immune activation via these toll-like receptors will also improve opioid analgesia and suppress opioid tolerance and dependence. Dr. Watkins then discussed how glial cell activation could give rise to the individualized manifestation of sickness responses characteristic of Gulf War illness (including fatigue, learning and memory problems, pain and anxiety).

Dr. Klimas, a VA clinician and meeting speaker, mentioned that various new therapeutics targeting glial cells are currently undergoing clinical trials.

Dr. Meggs asked Dr. Watkins to clarify what researchers cited on one of her slides meant by stating that they were using neuroimaging to evaluate Central Nervous System (CNS) pathway "integrities." Dr. Watkins replied that the researchers meant they were looking at how the given system being imaged (serotonin, norepinephrine, etc.) is functioning with respect to the disease process. These techniques will hopefully lead to earlier treatment of neurodegenerative diseases in the future.

Dr. Mariana Morris, an invited speaker and physiologist/neuroendocrinologist, asked if the effects of Dr. Watkins' toll-receptor mediated pain relief last for a long time, in the same way gene therapeutics do. Dr. Watkins replied that the current treatments she is working on do not involve gene therapy and would therefore be administered repeatedly as blood brain barrier permeable and orally available compounds.

Dr. Floyd Bloom, a member of the Committee, remarked that Dr. Watkins' synthesis of how these findings relate to Gulf War illness were perhaps the most persuasive of any hypothesis he has heard in all of the years he has been studying the illness. He asked if the toll-like receptor-4 (TLR4) that Dr. Watkins has been researching is involved in the therapeutic effects of low dose naltrexone. Dr. Watkins replied that she believes this to be true. She explained that because the toll-like receptor-4 is activated by opiates in a unique

way, (+)naloxone (an opiate antagonist) can be used to block glial activation without interfering with the analgesic effects of opiates acting on neuronal receptors. She believes a similar effect is carried out by low doses of naltrexone, but that unlike naloxone, naltrexone is dose-limited (meaning as doses are increased to compensate for increasing levels of pain it begins to interfere with the neuronal opiate receptors). Dr. Bloom followed up his first question by asking how Dr. Watkins' findings relate to the phenomenon whereby animals develop a tolerance to opiates in one environment, but when moved to another environment exhibit increased effects from the same dose. Dr. Watkins had no explanation, but expressed interest in the answer.

Reverend Joel Graves, a member of the Committee, asked Dr. Watkins to clarify whether the brains of people exposed to organophosphorous pesticides would exhibit a glial response. Dr. Watkins replied that if brain cells were stressed and damaged or killed that the glial response would be activated. Rev. Graves described his personal experience with Gulf War illness, specifically his tolerance to morphine. He expressed frustration at not having better treatment options than ibuprofen, which he takes daily for pain. Dr. Watkins replied that medical marijuana acts on cannabinoid receptors involved in pain modulation and she remarked that one drawback to medical marijuana is that it is a mixture of compounds, but that new synthesized drugs targeting specific cannabinoid receptors are currently under development. Dr. Watkins expressed hope that treatments for Gulf War illness could be developed, but explained that first the underlying neurochemical mechanisms of the illness must be understood. She is therefore very excited about the new neuroimaging techniques being proposed to study ill Gulf War veterans.

Dr. Fields then commented on the controversial use of medical marijuana, and the nonspecific nature of it compared to extracting or synthesizing individual cannabinoids found in marijuana so that they can be administered in measured doses of known potency. Dr. Klimas commented that a cannabinoid prescription drug has been approved in the US for increasing appetite in HIV patients.

Dr. Sullivan thanked Dr. Watkins for drawing connections between chronic pain and white matter changes seen in Gulf War veterans. Dr. Watkins replied that the connections go even beyond glia. She remarked that while astrocytes and microglia are certainly involved, other types of glia (e.g. oligodendroglia) and non-glial cells, including fibroblasts and endothelial cells in the blood vessels also play roles in immune signaling in the brain.

Ms. Diane Miller, an audience member from the Centers for Disease Control (CDC), asked if microglia have more of a role in priming than astrocytes do. Dr. Watkins replied that further and more robust research is needed to answer that question.

Dr. Steele asked if animal or early human studies reveal whether disrupting pain pathways can contribute to the alleviation of other symptoms common to ill Gulf War veterans. Dr. Watkins replied that different subsets of sickness responses definitely appear to be linked. She added that TLR4 receptors have been implicated in aging and

stress, and other research on learning, memory and anxiety is ongoing. Dr. Steele then asked if Dr. Watkins was aware of any scenario for initiating a priming state related to alterations in acetylcholine. Dr. Watkins replied that she was not aware of any, largely because the priming research was still very new, and that most of these studies have been done with peripheral immune cells. Dr. Steele asked if other neurotransmitters are being studied in the priming research. Dr. Watkins replied that she was currently collaborating on research investigating the role of α7 cholinergic receptors in neuropathic pain, but that no data specific to priming currently exists. Dr. Steele commented that some work looking at effects of low-dose sarin exposure suggests that the α7 cholinergic receptors are involved. Dr. Steele added that people with Chronic Fatigue Syndrome (CFS) tend to be very intolerant to alcohol, and she asked if Dr. Watkins thought this might involve their TLR4s. Dr. Watkins replied that she would be interested in analyzing tissues from those individuals, including Gulf War veterans. Dr. Klimas responded that brain, spinal cord and other tissues from at least several deceased Gulf War veterans exist in a growing national tissue bank. She then asked Dr. Watkins what was known about the safety of quieting glial activation. Dr. Watkins replied that risks are reduced because intrathecal administration is site-specific, and the substance is endogenous and has a short half-life.

Dr. Steele asked if blocking glial activation after the priming effect has been initiated could reverse the priming effect. Dr. Watkins said that she is currently undertaking research to answer this question.

Chairman Binns then thanked Dr. Watkins for her presentation and called for a 15 minute break. After the break, Dr. Sullivan introduced the next speaker, Dr. Peter Bass.

Microtubules and Neurodegeneration

Dr. Peter Baas, Drexel University

Dr. Baas spoke about the role of microtubules in neurodegenerative diseases (see Appendix A – Presentation 2). Dr. Bass explained how neurons rely on microtubules for structure and active transport before outlining various ways in which microtubule damage can be implicated in injury and disease. He and his research team planned to use a rat model of Gulf War (GW) illness to study potential underlying microtubule weaknesses and possible therapies to alleviate common symptoms of GW illness.

At the conclusion of Dr. Baas' presentation, Dr. Sullivan recalled research presented at a previous meeting that found greatly reduced size of axonal microtubules in organophosphate-exposed mice. She asked Dr. Baas if he felt that such a mechanism could explain reduced information processing and cognitive processing speeds. Dr. Baas replied that any agent that degraded the microtubules could exert that effect. He added that deficits tend to first be observed in the longer axons, and that clinical findings of ill Gulf War veterans might shed more light on which tracts were most severely affected.

Dr. Sullivan followed up by asking whether deficits occurring later in life related to microtubule functioning might also be related to mitochondrial functioning. Dr. Baas

replied that impaired axonal transport along microtubules could have far-reaching impacts, including decreased levels of mitochondria.

Dr. Sullivan then asked if antioxidants could potentially help improve functioning of thinning axons. Dr. Baas replied that he believed so, since molecular motor proteins are particularly susceptible to oxidative damage.

Dr. Bloom then asked Dr. Baas to say a few words about the microtubular system in glia. Dr. Baas replied that he had done some research on microtubules in oligodendrocytes (a type of glia), and that effects seen in neuronal microtubules would be relevant to potential effects in glial microtubules.

Dr. Sullivan thanked Dr. Baas for his presentation before introducing the next speaker, Dr. Nancy Klimas.

XMRV Virus, Chronic Fatigue and Gulf War Illness

Dr. Nancy Klimas, Miami VAMC

Dr. Klimas began her presentation by discussing the potential role retroviruses may play in CFS and Gulf War illness (see Appendix A – Presentation 3). She then reviewed the recent research findings on xenotropic murine leukemia virus-related virus (XMRV) in CFS. Dr. Klimas noted that the most recent finding suggests that this virus interacts with the endocrine system to increase the oncogenesis of XMRV. She also noted that no studies had yet determined whether the viral infection was active or latent. At the time of her presentation, Dr. Klimas was waiting on results from a study she had just completed on XMRV status in ill Gulf War veterans.

Dr. Klimas also outlined some important questions that need to be asked when trying to draw conclusions and design future studies based on the findings of the recent XMRV research. She asked whether blood was the best compartment to be looking for the virus in, and also wondered whether the methodologies being used were adequate and if they were consistent enough to warrant comparison between studies conducted by different research groups. Dr. Klimas remarked that efforts to validate recent findings and devise consensus methods for future studies were currently underway. With regard to XMRV's potential involvement in Gulf War illness, she emphasized the importance of considering co-infections, as well as various factors that may have triggered a latent virus to become active.

At the conclusion of Dr. Klimas' presentation, Dr. Meggs asked whether a sub-set of individuals formerly diagnosed with CFS might be recategorized as having a chronic XMRV infection as a result of the research that Dr. Klimas had discussed. Dr. Klimas replied that no causality could be drawn at this point about the presence of XMRV and symptoms of CFS in any patients. She recommended a four-arm intervention study in order to determine whether co-infection (e.g. with herpes or another virus) might be underlying CFS symptomatology in some individuals.

Dr. Dedra Buchwald, a member of the Committee, cautioned against drawing strong conclusions from the first positive study, especially in light of the additional negative study results produced by several other research groups. Dr. Buchwald critiqued the participant selection in the singular positive study, based on her perception that the study had included lymphoma patients. Dr. Klimas responded by stating that the critique to which Dr. Buchwald referred had misrepresented the study, and she clarified that none of the 100 study participants in the study with positive findings had lymphoma. Dr. Buchwald then critiqued the study's lack of demographic and diagnostic criteria, and also expressed concern that the samples were not shared with other researchers for validation. She added that the group in Nevada had a financial interest in the study results, since they are making the tests for the virus. Dr. Buchwald then called for careful interpretation and critical thinking with regard to the study results, especially given the half dozen studies which produced negative results.

Chairman Binns then drew the discussion to a close due to time constraints, thanking Dr. Klimas for her presentation. Dr. Sullivan then introduced the next speakers, Dr. Vidar Lehmann and Dr. Bjorn Knudtzen, two individuals representing a Gulf War illness research group from Norway.

Planned Survey of the Health Situation of Norwegian Gulf War Veterans

Dr. Bjorn Knudtzen, Norwegian Armed Forces Medical Services
Dr. Vidar Lehmann, Norwegian Armed Forces Medical Services

Dr. Knudtzen began his presentation by introducing his four colleagues, Dr. Gunnar Skipenes, Dr. Vidar Lehmann, Geir Stamnes, and Dr. Jo Kvello. He explained that some of the Norwegian veterans who fought in the Gulf War became ill after their service, and that in response Norway's Department of Defense had asked this group to submit a report at the end of the year to inform the government's forthcoming decisions and actions. Dr. Knudtzen expressed hope that the American research on Gulf War illness could inform his team's investigation and report.

Dr. Lehmann then spoke about, and showed pictures of, the exposures experienced by the Norwegian Gulf War veterans, and the relevant research that has been carried out in his country (see Appendix A – Presentation 4). He also explained that he and his colleagues were currently compiling a questionnaire for distribution to Norwegian Gulf War veterans that would help his team write their report.

Dr. White remarked on her research carried out on Gulf War veterans from Denmark, and offered to share her questionnaires with Dr. Lehmann's team. She mentioned that in this Danish cohort, pesticide-treated uniforms were the environmental exposure factor most related to being symptomatic. Dr. Lehmann replied that the Norwegian uniforms were not treated with pesticides, except for troops stationed in Al Jubail, Saudi Arabia.

Dr. Steele then asked why Norway had initiated the Gulf War research program (whether it was because of reported illness or as a precaution). Dr. Lehmann replied that a high percentage of the Norwegian Gulf War veterans were afflicted with symptoms similar to

those of ill Gulf War veterans in the US. Dr. Steele asked if the ill Norwegian veterans had served in a particular region. Dr. Lehmann replied that this review was currently underway. Dr. Steele also asked Dr. Lehmann to clarify if any Norwegian troops had taken pyridostigmine bromide (PB). He answered that although troops arriving after the war had ended did not take PB, the troops stationed in Al Jubail before the end of the war did.

Dr. Sullivan asked Dr. Lehmann if the Norwegian troops brought any insecticides with them to the Gulf War theater. He replied that some were brought, but not used systematically. He added that the records on file were not very detailed. Geir Stamnes, a Norwegian Gulf War veteran and colleague of Dr. Lehmann, commented that he and other troops that were part of the 1st Armored Division had been given equipment and pesticides by the British.

Mr. Stephen Robinson, a member of the audience, stated that he served in the Office of the Special Assistant for Gulf War Illnesses that investigated many of the issues around Al Jubail. He remarked that a considerable amount of information about US troops serving in that area was available, and asked if Dr. Lehmann had connected with anyone in the US Department of Defense to look at that information as part of his team's review. Dr. Lehmann said he would be interested in doing so, and that he would also be looking into the Kuwaiti civilian medical files from that time period. Dr. Steele commented on a study of Kuwaiti civilian health currently underway at the Harvard School of Public Health.

Dr. Sullivan and Chairman Binns thanked Dr. Lehmann and his colleagues before breaking for lunch. After lunch, Dr. Sullivan introduced the next speaker, Dr. Robert Haley.

UTSW Neuroimaging Studies Update

Dr. Robert Haley , University of Texas Southwestern & VA Dallas Healthcare System

Dr. Haley discussed the most recent findings from his research group's multi-modal imaging study (see Appendix A – Presentation 5). First, Dr. Haley discussed imaging techniques as tools for revealing pathogenesis, then he talked about additional studies that his research group has been conducting in order to discover what the brain is doing when Gulf War veterans experience various symptoms. Symptoms that Dr. Haley has studied in Gulf War veterans using fMRI include memory deterioration, attention/concentration problems, impaired word finding, constant body pain, subtle motor control problems, chronic fatigue and personality change. Dr. Haley concluded by discussing the case study of an ill Gulf War veteran.

Dr. Meggs asked Dr. Haley if the changes over time seen within syndrome groups of the N-acetyl-aspartate (NAA) study corresponded with clinical deterioration. Dr. Haley replied that aging in the syndrome 1 group might have contributed to changes in NAA concentration seen, and that the veterans in this syndrome group subjectively reported worsening symptoms.

Dr. Buchwald remarked that Dr. Haley's finding that ill Gulf War veterans appear to recruit larger areas of the brain to perform a given task seems to parallel findings in patients with fibromyalgia who recruit larger areas of the brain when experiencing pain. Dr. Buchwald was puzzled by Dr. Haley's finding that activity in the amygdala was diminished in one cohort of ill Gulf War veterans, since the amygdala is involved in chronic pain, which most ill Gulf War veterans experience. Dr. Haley replied that further replication of findings was needed. Dr. Buchwald then remarked that diagnostic tests for Gulf War illness were still a long way off. Dr. Haley agreed, stating that the next step should involve thorough data analyses.

Dr. Steele then asked Dr. Haley if the findings of the physostigmine challenge test indicated anything about acetylcholine levels or cholinergic signaling in the brains of ill Gulf War veterans. Dr. Haley replied that the findings in one subset of ill Gulf War veterans paralleled those in patients with Alzheimer's Disease (which involves cholinergic abnormalities), but that the mechanisms were still not understood.

Dr. Klimas then commented on Dr. Haley's hippocampal imaging studies, and asked if any literature on transient amnesia suggests possibilities for recovery. Dr. Haley was not aware of any promising research of that nature. Dr. Klimas then remarked on a Dutch study in which patients with CFS who had reduced brain mass in areas associated with cognitive processing were able to regenerate some brain mass in response to cognitive behavioral therapy (CBT). Dr. Klimas then asked if Dr. Haley had any blood samples taken from patients before and after the physostigmine challenge experiments. Dr. Haley replied that there were blood samples taken before the challenge that were still being stored.

Dr. Sullivan asked if Dr. Haley had looked at human paraoxonase-1 (PON1) levels in each of his subgroups of ill Gulf War veterans, and if so whether they differed between each group. Dr. Haley replied that samples had been taken but not yet analyzed for PON1 levels.

Dr. Sullivan then introduced the next speaker, Dr. Mariana Morris.

Long-Term Health Effects from Sarin Exposure

Dr. Mariana Morris, Wright State University

Dr. Morris spoke about the cardiovascular effects of exposure to low doses of sarin in clinical and animal studies (see Appendix A – Presentation 6). Dr. Morris explained that doses of sarin too low to cause overt symptoms were capable of producing delayed, lasting, clinically relevant effects on cardiovascular functioning in mice. Dr. Morris also spoke about the effects observed in the catecholamine system in the brainstem, which is responsible for controlling autonomic functioning. She also mentioned a recent case-study of sarin poisoning in an Iraq war veteran that she thought should be followed up by the Committee.

Dr. Meggs asked if the chemical changes seen in Dr. Morris' research could be secondary to chronic neurogenic dysregulation of the heart, or if sarin could be acting through some direct mechanism to produce cardiovascular effects. Dr. Morris replied that the exact etiology is not yet known.

Dr. White commented that particulate matter also affects the autonomic nervous system and causes heart rate variability changes.

Rev. Graves asked Dr. Morris about the symptomatology of the sarin-exposed Operation Iraqi Freedom (OIF) veteran that she mentioned in her presentation. Dr. Sullivan remarked that he had suffered immediate poisoning, but that chronic neuropsychological symptoms were later reported. Dr. Morris commented that cardiac studies in this and other similar individuals could produce valuable information. She then asked Dr. Haley if he had done any cardiovascular measurement in his recent studies. He replied that he had not done extensive cardiovascular testing in his cohort.

Dr. Steele asked if Dr. Morris knew whether the types of changes she had seen in the mouse model were associated with any other type of clinical conditions. Dr. Morris replied that all heart syndromes could be implicated in the types of changes she observed in her mouse model. Dr. Steele commented that although heart disease has not been linked to Gulf War service, it has been understudied. She added that of all the hospitalization studies conducted by the Naval Health Research Center, a slight increase in hospitalizations for cardiomyopathy was observed in Gulf War veterans.

Chairman Binns then thanked Dr. Morris for her presentation and called for a 15 minute break. After the break, Dr. White began the discussion on the Committee's 2009 annual report.

Committee Discussion: 2009 Annual Report

Dr. Kimberly Sullivan, Committee Scientific Coordinator

Dr. White provided a brief background on the Committee's decision to issue annual reports (rather than more lengthy multi-year reports). She expressed hope that these more focused syntheses might identify advances in understanding illnesses associated with Gulf War service. Dr. White then called on Dr. Sullivan to present an overview of the contents of the 2009 report draft, so that input and feedback could be garnered.

Dr. Sullivan outlined the topics addressed in the 2009 Committee report and led a discussion of the proposed recommendations to be included in the document (see Appendix A – Presentation 7). After her presentation, Dr. Sullivan asked for feedback from the Committee.

Dr. Jack Melling, consultant to the Committee, responded that he would like to see future Committee reports explicitly state how new findings either reinforce or contradict the findings of the Committee's 2008 report. Dr. Sullivan agreed with the merits of this suggestion.

Dr. Bloom recommended starting the report with a short summary of the 2008 report's conclusions and recommendations (currently found at the beginning of the second part of section two in the 2009 report). Dr. Bloom also suggested revising the treatment section to reflect the fact that many of the proposed treatments presented to the Committee in 2009 are far from being ready for use, as he believes many will not stand the test of time. He cautioned against including references to specific mechanism-based treatment trials in the report, so as to prevent readers of the public from drawing overly positive conclusions about the current therapeutic options for ill Gulf War veterans. Dr. Sullivan agreed. Dr. Bloom then stated that some mechanism-based treatment ideas (including Dr. Watkins' presentation) did sound promising to him.

Dr. Steele seconded Dr. Melling's comment, remarking that the 2009 report already does begin to take this type of approach (building on and responding to, rather than restating, the findings of the 2008 report). Dr. Steele then suggested that some of the items in the body of the 2009 report be called something other than recommendations, unless they belong in the formal recommendations section. Dr. Sullivan replied that many of these "recommendations" might more appropriately be called "summaries" or "conclusions."

Dr. Buchwald remarked that one way to disseminate the Committee's findings to a broader venue of people while simultaneously providing a cautionary review could be put forward as an update to be published in a journal. Dr. Sullivan liked the idea but was concerned that this might violate the mandate which prevents the Committee from doing research. Dr. Goldberg remarked that the Committee's role was to provide recommendations to the Secretary. Chairman Binns agreed that the appropriate channels would need to be taken, but that he supported the need to raise awareness of and interest in Gulf War Illness among the scientific community.

Dr. Bloom asked Chairman Binns if anything was known about the status of the IOM report due to be presented to the VA. Chairman Binns replied that the latest he had heard was that the report release – which had originally been due in February – had been pushed to sometime in March.

Dr. Steele asked whether the Committee should include updates on all federal Gulf War research program activities in its annual reports. Dr. Sullivan replied that this was an issue worth considering.

Rev. Graves pointed out the importance of wording with regard to conclusions found when comparing non-deployed Gulf War veterans to all deployed Gulf War veterans versus exposure sub-groups of deployed veterans. Dr. Sullivan agreed with the importance of this distinction. Chairman Binns remarked that the document should remain open for comments from members. He also called for Dr. Steele's question regarding clarification of recommendations versus conclusions to be taken up by the Committee. Dr. White agreed with Dr. Steele that the integrative conclusions which have some suggestions in them should be called something other than recommendations.

Chairman Binns remarked that the recommendation section included edited versions of some of the recommendations discussed at the November 2009 meeting. He then requested that a recommendation be included which calls for making the best use of the work already done to date at UTSW. Chairman Binns placed particular emphasis on the need to build on the findings from UTSW animal studies. Dr. Sullivan said that this recommendation could be added into the report. Dr. Bloom supported this decision, after recalling that a discussion of these matters had taken place between the Committee and Dr. Kupersmith (VA's Chief Research and Development Officer) at the previous meeting in November 2009.

Dr. Buchwald asked if words such as "considerations" and "suggestions" could be used in place of "recommendations." Chairman Binns clarified that all the comments made on the last few pages of the 2009 report draft had previously been submitted or posted as recommendations. He then expressed his support for the decision to change the terminology of "recommendations" made in the previous sections.

Dr. Steele remarked that the 2008 report contained many recommendations, and that she saw some of them reflected in the 2009 report, but that new concerns had also been raised. She asked how a balance should be struck between broad and specific recommendations. Dr. Sullivan replied that the 2009 report included some broad recommendations simplified from the versions outlined in the 2008 report because of the VA's ongoing creation of a new Gulf War research program. Dr. Sullivan then said she was open to refocusing the recommendations if the Committee so desired.

Chairman Binns agreed with Dr. Bloom's recommendation to build on the findings and recommendations made in the 2008 report, focusing on updates specific to 2009. Dr. White then requested that a deadline be set for Committee comments. The deadline was then set for March 15, 2010.

Chairman Binns thanked Drs. Sullivan and White for organizing the meeting while simultaneously drafting the 2009 report. Chairman Binns then opened the floor to public comments.

Public Comments

Maj. Denise Nichols, a Gulf War veteran, provided an overview of the Gulf War obituaries. She asked for continued efforts to disseminate information to the veterans so that they could share research findings and Committee documents with each other and their doctors.

At 4:43pm Chairman Binns thanked the Committee, speakers and attendees before adjourning the meeting for the day.

DAY 2

Chairman Binns called the meeting to order on Tuesday, March 2, 2010 at 8:30am. Dr. Sullivan then introduced the first speaker of the day, Dr. Gudrun Lange.

War-Related Illness and Injury Centers (WRIISCs) Research Program Update

Dr. Gudrun Lange, DVA NJ Healthcare System

Dr. Lange began her presentation by welcoming the directors of the War-Related Illness and Injury Centers (WRIISCs) in Palo Alto, California, and Washington DC. She then provided a brief review of the national WRIISC program before updating the Committee on Gulf War research being conducted at the WRIISCs and discussing the clinical services, education and outreach efforts of the WRIISCs (see Appendix A – Presentation 8). According to Dr. Lange, seven WRIISC studies related to Gulf War veterans are currently underway, and another six studies have been proposed or are being planned. Dr. Lange explained that each WRIISC will be utilizing its particular area of research expertise to advance clinically applicable research into Complementary and Alternative Medicine (CAM) treatments (Washington DC WRIISC), brain imaging studies (DC and Palo Alto WRIISCs), genetic studies (Palo Alto WRIISC) and cardiovascular and vestibular studies (New Jersey WRIISC). In addition to conducting research, the WRIISCs perform comprehensive standardized medical evaluations of medically unexplained symptoms for veterans from any era or conflict. These evaluations include comprehensive exposure assessments, which can be conducted in person or over the phone. Dr. Lange explained that risk communication and education components are integral to all WRIISC research activities and clinical services. She concluded by providing an example of how research and clinical practice inform each other within the WRIISC model.

Dr. Meggs asked if recent research has led from the perception of Gulf War illness as a "medically unexplained syndrome" toward an understanding of it as chronic sequelae of organophosphate exposures. Dr. Lange replied that although she does not believe causation can be determined, correlational evidence has greatly informed the clinical medical community and their understanding and treatment of ill Gulf War veterans.

Mr. Anthony Hardie, a member of the Committee, asked if Dr. Lange could comment on the best way for veterans' service organizations (VSOs) to disseminate information on how veterans could go about getting clinical evaluations through a WRIISC and/or participate in WRIISC research. Dr. Lange replied that ill veterans' primary care providers can call the WRIISCs to set up evaluations for their patients. She added that individuals from WRIISCc are happy to travel to locations throughout the country to discuss research opportunities.

Mr. Steve Smithson, a member of the Committee, mentioned that Dr. Lange had previously commented on referral problems in the VA medical centers involving staff members and physicians being unaware of the WRIISCs and their programs. He asked if this continued to be a problem. Dr. Lange replied that some VA doctors still did not know

about the WRIISCs, but education and outreach efforts had been increasing, with help from veterans informing their doctors.

Mr. Hardie asked if the WRIISCs had a toll free number or website and Dr. Lange replied that she would provide that information to the Committee before the conclusion of her presentation.

Chairman Binns asked whether the veterans coming through the clinical program were all out-patients. Dr. Lange replied that each WRIISC has developed its own clinical system. In New Jersey, the clinical program is based on an out-patient model. The other two WRIISCs (in California and Washington, DC) have developed more in-patient programs. Dr. Lange expressed confidence in the comparability of the components of all programs.

Dr. Buchwald asked about the geographic distribution of veterans across the United States, expressing concern that the Palo Alto WRIISC serves more than half of the country's land mass, which may pose financially prohibitive for veterans traveling from far away who must pay for their transportation. Dr. Lange replied that most Gulf War veterans were located on the east coast, and that equal distribution had been considered in the creation of the Palo Alto WRIISC.

Dr. Steele asked about the purpose of the exposure evaluations, and what role was served by the final WRIISC report issued to each evaluated veteran. Dr. Lange replied that often veterans were grateful simply for receiving explanations of the clinical evaluations and exposure assessments. She added that the reports issued by the WRIISCs could not be used for compensation and payment purposes.

Chairman Binns thanked Dr. Lange and the individuals who had come to the meeting from the other WRIISCs. He expressed hope that communication could be maintained so that any clinical findings from the WRIISCs might be used to inform the Committee's research understanding.

Chairman Binns then asked if any evidence – anecdotal or otherwise – had emerged from the WRIISCs regarding the effectiveness of yoga and acupuncture in alleviating symptoms in ill Gulf War veterans. Dr. Bonnie Benetato, the Deputy Director of the WRIISC in DC, replied that the complementary and alternative medicine (CAM) program at the WRIISC in Washington, DC had begun several years ago, and that 18 percent of the veterans seen in the program served in the Gulf War. Dr. Benetato also said that anecdotal evidence suggested that these veterans were experiencing relief from symptoms of pain as a result of yoga and acupuncture treatment offered at the Washington, DC WRIISC. She also mentioned that brain imaging and behavioral outcomes were being measured in ongoing research, and that a study of CAM therapies in PTSD-related insomnia was currently underway.

Dr. Sullivan asked if Richard Niemtzow's ear acupuncture protocol was being used. Dr. Benetato replied that the traditional 5 point protocol was in use, but that she did now know if it was Dr. Niemtzow's exact protocol.

Dr. Sullivan then introduced the next item on the agenda, which was an update on the Gulf War Veterans Information System (GWVIS).

GWVIS report and tracking update

Lois Mittelstaedt, Chief of Staff, VBA Office of the Under Secretary for Benefits

Ms. Lois Mittelstaedt, Chief of Staff of the Office of the Under Secretary for Benefits in the Veterans Benefits Administration, updated the Committee on the GWVIS report and tracking progress. Ms. Mittelstaedt first spoke about the difficulties involved in the ongoing, phased inter-system conversion of records for the 3.5 million veterans receiving disability compensation and pension benefits. She also commented that changes by which information is acquired from the Department of Defense (DoD) were underway. Ms. Mittelstaedt told the Committee that by the end of the next quarter the next GWVIS report would be out, and that it would include greater levels of detail than previous reports as a result of the system transitions she discussed.

Dr. Steele expressed her and others' concern that in past GWVIS reports had listed only 3,000 Gulf War veterans as being service connected for undiagnosed illnesses, and that 70 percent of veterans applying for benefits were rejected. She asked if the transition discussed in Ms. Mittelstaedt's presentation would result in dramatic changes in these numbers of documented claims and service connections. Ms. Mittelstaedt did not believe individuals had been undercounted, but that increased specificity of diagnoses would be achieved under the new system.

Mr. Smithson asked if the August 2008 report was the last issued report. Ms. Mittelstaedt replied that the August 2008 report was the last report to include undiagnosed illnesses, and that issues with inconsistent coding had to be corrected in order for accurate data on undiagnosed illness claims and compensation to be determined. Mr. Smithson asked when the next updated report was due out, and Ms. Mittelstaedt said the goal was no later than the end of June 2010. Mr. Smithson then asked if the wide email distribution of GWVIS reports to VSOs would be resumed and Ms. Mittelstaedt replied that they would.

Mr. Hardie requested that the GWVIS data be updated on the VA Gulf War website as well. Ms. Mittelstaedt agreed that this would be a good idea.

Dr. Sullivan asked if any information on the breakdown of disability claims (e.g. number of claims filed for CFS, irritable bowel syndrome, etc.) could be included in future reports. Ms. Mittelstaedt replied that the new diagnostic coding system would allow for greater specificity of that nature. Dr. Sullivan and Dr. Steele then asked about the possibility of including statistics on death and hospitalization rates, respectively. Ms. Mittelstaedt replied that VBA does not have that data.

Mr. Hardie then added that the community of Gulf War veterans was very interested in separating out the undiagnosed illness claims from those for CFS, fibromyalgia and

irritable bowel syndrome. He also expressed interest in knowing the unique number of veterans and the breakdown of their claims.

Chairman Binns then invited members of the audience to ask questions.

Maj. Nichols expressed her concern that the data from Operation Desert Storm (1991) be kept separate from the Operation Enduring Freedom/Operation Iraqi Freedom (OEF/OIF) data. Ms. Mittelstaedt explained that even if the data were combined in a single report (which they currently are not) the cohorts would not be combined.

Mr. Smithson then asked how the undiagnosed illness claims were being tracked, and whether the OEF/OIF veterans would be distinct from the Persian Gulf War I veterans. Ms. Mittelstaedt replied that the only issue that might arise would be in teasing out whether illnesses in veterans who served in both wars were attributed to their OEF/OIF or Persian Gulf War service. Mr. Robinson then asked if the system could be adjusted in order to recognize the difference between time periods for veterans who served in several wars in a particular theater. Ms. Mittelstaedt replied that identifying the origin/time period of disabilities in this way is not part of the system for those veterans who served in multiple wars in the same theater (OEF/OIF and Gulf War I).

Chairman Binns then called a two-minute break, after which he introduced the VA Chief of Staff, Mr. John Gingrich.

VA Gulf War Task Force

Mr. John Gingrich, VA Chief of Staff

Mr. Gingrich began by stating that he would not be able to discuss the detailed findings of the forthcoming Gulf War Task Force report because it had not yet been made public. He explained that the report was currently being revised based on feedback from other executive branch departments and that these revisions would be sent to the Office of Management and Budget for review by the end of the week. Mr. Gingrich stated that once feedback was received from DoD the report would be made available online for a 30 day period of public comment.

Mr. Gingrich stated that a background brief summarizing topics and ideas from the report had been made public on February 26, and he then outlined some of the recommendations therein (see Appendix B). He discussed the need for improved partnerships, including greater collaboration between the VA and DoD, and he also spoke of the need for increased transparency and searchability of the VA records system. Mr. Gingrich then outlined some of the ongoing updates being implemented throughout the VA, including website changes, medical staff training material revisions and improved medical surveillance of veterans who may have been exposed to hazardous substances. He also mentioned that the VA would be holding seminars on environmental exposures related to the Gulf War and other military service. Mr. Gingrich also mentioned that a

telephone survey of veterans was being planned in order to get feedback on improving VA outreach and communications.

Dr. Steele applauded Mr. Gingrich and the efforts he and others at the VA had recently taken to bring about positive changes to the system. Chairman Binns then thanked Mr. Gingrich for his encouragement of the culture change necessary to bring about reform. He then asked for individual Committee members to provide feedback to Mr. Gingrich, noting that feedback to the Task Force report would also be coming from individual Committee members rather than the Committee as a whole, since the Committee would not be meeting in a public forum until after the end of the 30 day period of public comments on the report.

Rev. Graves recommended that any non-Gulf War issues (e.g. Camp Lejeune) be kept in a separate section of the report in order to maintain the focus and integrity of the Gulf War Task Force. He also said he would like to see the statistic that 25 percent of Gulf War veterans suffer from chronic illness listed in the report. Rev. Graves also remarked that he was dismayed by the mention of cognitive behavioral therapy (CBT) being used for Gulf War veterans via telephone, due to his prior experience with the VA presuming his symptoms were due to post-traumatic stress. Mr. Gingrich replied that by law, the Gulf War began on August 2, 1990 and continues today, and thus the Task Force must be cognizant of the implications its report and all of its recommendations have on any veterans serving in the Persian Gulf theater during that broad time period.

LTC Adam Such, a member of the Committee and veteran of the Gulf War and other conflicts, then acknowledged the difficulty of the task that Mr. Gingrich was tackling.

Dr. Bloom said that he was encouraged by Mr. Gingrich's comments and then remarked on the previous day's presentations to the Committee, noting that he and others had been inspired by the ability of science to some day solve the health problems of ill Gulf War veterans.

Mr. Hardie said he was greatly encouraged by the opportunity being given for public input, and then echoed Rev. Graves' concern that the focus of the Task Force report be on Gulf War veterans who served during 1990 and 1991. He added that other veterans who had served during that time period in areas outside the official Gulf War theater (e.g. Kyrgyzstan and Afghanistan) had also been exposed to burn pits and other environmental exposures. Mr. Hardie also expressed the concern voiced to him by another veteran over the disconnect between the excellent care provided at the WRIISCs and the ability (or lack thereof) of veterans being able to get to the WRIISCs and receive direct communication from the WRIISC doctors. Mr. Gingrich replied that if Mr. Hardie provided him with the individual's name he would see that the individual's concerns were addressed.

Dr. Buchwald commended Mr. Gingrich for the positive movement toward a progressive approach to medical care for Gulf War veterans, who wish to receive holistic, individualized care without stigma. As a primary care provider herself, Dr. Buchwald

asserted that many primary care providers are not well informed and that they often don't communicate well. She thanked Mr. Gingrich for encouraging a culture change that she believes will help address some of these issues.

Mr. Smithson stated that he was looking forward to reading the report when it comes out.

LTC Marguerite Knox, a member of the Committee, expressed her gratitude for Mr. Gingrich's attitude toward veterans, then she commented on Rev. Graves' remarks regarding the number of Gulf War veterans suffering from multisymptom illnesses. She said that she hopes to see this and related statistics in the benefits section of the final Task Force report. Dr. Goldberg interjected to state that he has read the Task Force report and that he thinks the background briefing has generated some misconceptions about the report, which he believes Committee members will be very satisfied with. Mr. Gingrich then commented that the full report would soon be posted for public viewing and a 30-day comment period.

Dr. Meggs, in agreement with Rev. Graves, expressed concern that the hazards and exposures unique to the 1990-1991 war be accounted for in light of the law which includes OEF/OIF veterans in the Gulf War.

Dr. Steele commended Mr. Gingrich for his approach before asking Mr. Gingrich to clarify whether the Veterans Health Initiative (VHI) training program for VA doctors has been modified and finalized. Mr. Gingrich replied that it had not yet been finalized, but would hopefully be done in April. Dr. Steele expressed her concern that the training materials were not just outdated but that their content in the past had been selective in a way that misrepresented the large body of existing research. She asked how the revised VHI content had been compiled, and whether any process for review existed such that she and other members of the Committee might be able to improve its quality if necessary. Mr. Gingrich replied that he would have to go back to ask the individuals responsible for revising the VHI content.

Dr. Sullivan spoke about her experience evaluating Gulf War veterans at the Boston VA and expressed her concern that the clinicians there had very little understanding of the effects environmental exposures have on cognition and health in general. She therefore emphasized the importance of revising the training manual. Mr. Gingrich agreed, adding that the environmental exposure seminars should help as well.

Dr. White emphasized a concern she had about a disconnect between clinical training and the use of exposure assessment tools that she fears may be resulting in missed clinical diagnoses.

Dr. O'Callaghan urged Mr. Gingrich and others to revisit the failings of the contracting mechanism at UTSW in order to determine how such problems could be avoided in the future. He also expressed hope that some of the animal-based research studies begun at UTSW would not be completely lost as a result of discontinued funding.

Dr. Melling stated that the proceedings from both days of the meeting had been very encouraging. He congratulated Mr. Gingrich and his colleagues on recognizing that the system needed fixing.

Dr. Golomb echoed Dr. Bloom's comments on the promise of science, then spoke about the concerns she had regarding the VA's training program. As a VA clinician, Dr. Golomb underwent this training (which she referred to as the VA's education module), and she stated that she felt the training reflected and contributed to adverse attitudes toward Gulf War veterans on the part of VA employees. She emphasized the importance of having individuals with updated expertise and the right attitudes review the training documents for content and approach.

Chairman Binns thanked Mr. Gingrich and suggested that the Committee's comments regarding a need for reviewing the clinical training materials might also apply to the benefits training materials, though the members off the Committee might not be the most qualified experts in that area. Chairman Binns then called for several brief questions from veterans in the audience.

Mr. Robinson thanked Mr. Gingrich and asked that the Secretary and others at the VA work in partnership with the Committee to draft reports prior to their public release and review.

Maj. Nichols expressed her concern that VA registries be improved with regard to documenting Gulf War exposures and the health of Gulf War veterans' children. Maj. Nichols also encouraged Mr. Gingrich to capture and disseminate more proceedings such as the current meeting, both to veterans and to doctors treating veterans, in digital (video) format if possible. Maj. Nichols' last comment was a request for round table events to be held at VA offices throughout the country, so that veterans could participate more directly and at earlier stages.

In response to Maj. Nichols' call for improved communications and videocasting, Ms. Miller commented that YouTube contains lots of scientific information that might make the technical content of Committee meeting proceedings more accessible to veterans and others in the non-scientific community.

Chairman Binns then asked if Mr. Gingrich had any concluding remarks. Mr. Gingrich said that he looked forward to receiving feedback, and that he and Secretary Shinseki strongly believe that the VA has a long-term obligation to all individuals who are sent to war. He thanked the Committee for advocating on behalf of Gulf War veterans, and for helping the VA improve their services and approach.

Chairman Binns called for a short break before welcoming Dr. Joel Kupersmith.

VA Gulf War Research Program Development

Dr. Joel Kupersmith, Chief Research and Development Officer, Department of Veterans Affairs

Dr. Kupersmith began the discussion by giving an overview of the progress made on drawing up an organizational chart for the VA's Gulf War Research Program. He remarked on a series of discussions he had recently had with Committee members and other scientists in the field, and he then stated that a decision had been made to create a steering committee that would have nine members. Four of these members would be nominated by (and could be members of) the Committee, another four members would be nominated by the VA's National Research Advisory Committee, and a chairman would also be selected. His understanding is that the steering committee would technically report to the Committee and to the National Research Advisory Committee. Dr. Kupersmith then spoke about the formation of a planning committee to oversee a cohort of Gulf War research subjects that will be involved in a variety of clinical research trials under the VA's Cooperative Studies Program (CSP). Before asking for questions and comments Dr. Kupersmith also mentioned that he and the Office of Research and Development (ORD) was currently attempting to find a toxicologist to be part of the Gulf War Research Program.

Chairman Binns then asked for comments from members of the Committee who had been involved in the conference calls with Dr. Kupersmith and members of the Secretary's personal staff regarding the new VA program.

Dr. White commented on the challenge of recruiting the best, brightest scientists who are most knowledgeable about Gulf War illness, both inside and outside of the VA. She reflected positively on the guidance and oversight role that the Gulf War steering committee would have in relation to the VA's Gulf War projects in the CSP and ORD.

Dr. Melling remarked that the structure of the steering committee would be critical, and that it would need to include enough knowledgeable people with broad, non-partisan views in order to avoid special interests being pursued. Dr. Kupersmith replied that this would be ensured through the National Research Advisory Committee's guidance. He also commented on the importance of having creative input, and the necessity of encouraging the involvement of new investigators.

Dr. O'Callaghan asked Dr. Kupersmith if he could comment further on the recruitment of the toxicologist, and how the individual would interact with the steering committee once found. Dr. Kupersmith said that he could not divulge details beyond explaining that the individual would be working with the steering committee, with connection to the ORD.

Dr. Steele asked Dr. Kupersmith if and how the steering committee would decide what research gets funded, how the Requests for Applications (RFAs) would be developed, what the content of the RFAs would be, and who would be reviewing the research proposals. Dr. Kupersmith replied that the steering committee would advise the ORD, which would make the ultimate decisions and take responsibility for the Gulf War

Research Program. He added that the steering committee would work by internal consensus (not majority voting), and consensus with the ORD. He envisioned the committee meeting several times per year face-to-face, with more frequent telephone and possibly web-based meetings throughout the year. Dr. Steele responded by expressing that her concern lies less with the workings of the steering committee and more with the program's procedural activities and effectiveness, and restated her question about the RFA process. Dr. Kupersmith replied that the steering committee would make recommendations to the CSP planning committee, which would then be responsible for writing RFAs and/or planning research through the CSP. Dr. Kupersmith emphasized the important role the steering committee will play in coordinating with the Department of Defense CDMRP Gulf War research program. He reminded the Committee that the Deployment Health Working Group had been charged with integrating all research for many years.

Dr. O'Callaghan asked what the procedure would be for reviewing RFA proposals in new areas of research that looked promising, but in which the steering committee and VA lacked expertise. Dr. Kupersmith replied that the Congressionally Directed Medical Research Programs (CDMRP) and NIH could be very helpful in such instances.

Dr. Bloom then made two suggestions. First he first remarked that it was an opportune time to recruit new people into the field because the 1 and 2 year NIH stimulus grants would soon end. Secondly, Dr. Bloom recommended that Dr. Kupersmith consider looking into the principles of the stem cell program at the California Institute for Regenerative Medicine, where 3 billion dollars had been funneled into training scientists to conduct stem cell research that may be relevant to the Gulf War Research Program.

Mr. Hardie encouraged Dr. Kupersmith to consider expanding the steering committee to include one or more Gulf War veterans. Dr. Kupersmith remarked that the National Research Advisory Committee does have veteran representation.

Chairman Binns commented on two pieces from the previous day's meeting which he thought were particularly notable. The first was the glial cell research being done at NIH and the University of Colorado which he stated offers both a mechanistic explanation of illness, and hope for treatment in the not-too-distant future. Secondly, Chairman Binns remarked on the importance of building on the history of Gulf War research conducted at the VA, UTSW, and other places. Dr. Kupersmith agreed with Chairman Binns.

Dr. Goldberg then remarked that although the Gulf War Research Program would be an internal "intramural" program open to VA scientists, non-VA scientists would have the opportunity to participate in the program if they became part of the VA. Dr. Golomb then asked if the VA could revisit the possibility of allowing Principal Investigator (PI) exceptions so that non-VA PIs (such as herself) could lead teams of VA researchers. Dr. Kupersmith replied that the integrity of the intramural program had to be maintained, and that doing so would not be best from both a legal and a research stance.

Dr. Goldberg then drew the Committee's attention to the final FY2009 and projected FY2010 documents summarizing the ORD funding for ongoing Gulf War research projects (see Appendix C, Documents 1 & 2), noting that the 2010 projects would not be finalized until early 2011. Dr. Goldberg also announced that the 2008 report had been publicly posted on the VA website, and that printed copies should be available by the next Committee meeting in June 2010.

Dr. Steele expressed concern that of 12 million dollars projected to be spent in 2010, $11 million would be going to one investigator. Dr. Goldberg explained that none of the projects listed on the 2010 document had been reviewed yet, but would be reviewed in April 2010. Dr. Steele then asked how the project received funding. Dr. Goldberg replied that the project in question was actually an instrument request for new high powered imaging equipment (2 new MRI machines, including one 7 Tesla magnet). Dr. Steele asked if the project, led by Dr. Michael Weiner, was considered to be Gulf War illness research, and Drs. Kupersmith and Goldberg replied that it was. Dr. Kupersmith expressed that he has confidence in Dr. Weiner's research ability and dedication to studying Gulf War illness. He stated that he hoped to add more programs to the list once the recently submitted RFAs had been reviewed. Dr. Steele replied that she did not feel that the lion's share of the Gulf War funding should be going into imaging equipment. Drs. Kupersmith and Goldberg argued that the money going to fund this equipment would not take away from funding for other projects yet to be reviewed. Dr. Steele replied that she believed many other research models could have been funded within the timeframe necessary for the $15 million budget allotment. Dr. Kupersmith responded by asserting that new, higher technologies such as the 7 Tesla magnet were justifiable investments in the future of Gulf War research. Dr. Golomb emphasized her concern that such a large amount of "Gulf War research" money was being spent on equipment that was not exclusive to Gulf War research.

Mr. Hardie then expressed his frustration that the MRI machines were being categorized under "Gulf War research" funding, though he did agree that Dr. Kupersmith's justification for investing in the equipment was compelling. He added that when Dr. Haley's research contract was cancelled, veterans were promised that the resultant funding would go toward other similar research. Mr. Hardie expressed disappointment that this funding had been allotted to these MRI machines in the name of Gulf War research. Dr. Kupersmith acknowledged Mr. Hardie's concern.

Dr. Melling expressed his understanding of the funding decision, and added that he hoped it would encourage people within the VA system who have access to that enhanced technological power to pursue Gulf War research in the years ahead. Dr. Kupersmith commented that he hoped it would also attract researchers from outside the VA to become part of the VA research program.

Dr. Wes Ashford, Director of the Palo Alto WRIISC, remarked that he had been interested in Gulf War Illness for 15 years and that he has used imaging techniques to study ill Gulf War veterans in the past. He added that he has access to a 7 Tesla MRI machine and would like to possibly collaborate with Dr. Weiner by conducting

complementary imaging studies at his WRIISC using PET, CT and MRS imaging techniques. Dr. Kupersmith appreciated Dr. Ashford's comment.

Dr. Golomb then suggested that since the money had been allocated to the MRI equipment under Gulf War research funding, perhaps a formal mechanism could be introduced so that researchers wanting to use the machine to conduct Gulf War related research would get priority over non-Gulf War researchers desiring to use the equipment. Dr. Kupersmith remarked that this was a valid point.

Chairman Binns then clarified that the Committee's objections were not against Dr. Weiner receiving the funding, but that such a large sum of Gulf War money was being spent on imaging equipment. He remarked that the Committee has generally felt that a disproportionate amount of Gulf War illness funds had gone to medical imaging. Chairman Binns then commented that this was one of the central themes of the Committee's recommendations regarding the Gulf War research program in Texas. Chairman Binns added that it was his understanding that 7 Tesla magnets were generally used for animal imaging. Dr. Ashford remarked that the 7 Tesla magnet at Stanford was being used for human research. Chairman Binns then strongly encouraged that ORD reconsider the $11 million allotment, mentioning the Committee's discontent with the process through which "Gulf War" research had been exaggerated in the past, including previous "Gulf War" funding which mostly supported ALS research. Dr. Kupersmith replied that ORD would be funding other technologies (e.g. genomics) but that cutting edge imaging would remain a major focus.

Dr. Kupersmith then spoke to Rev. Graves' concern that Gulf War veterans would react negatively to CBT initiatives due to stigma they had experienced over the years. He expressed confidence in the ability of CBT to treat conditions with combined genetic and environmental origins, and then discussed the need to break through the stigma by supporting cutting edge scientific technologies that would attract intelligent new researchers to the field of Gulf War research.

Chairman Binns replied that he would have liked to see the $11 million spent differently, especially in light of the fact that comparable imaging facilities were already available at Stanford, 35 miles away from Dr. Weiner. Dr. Kupersmith objected to the assumption he felt Chairman Binns was making about the inability of the VA to spend additional money on Gulf War research in FY2010. He explained that time (not funding) was the limiting feature, and that additional projects could be funded for FY2010. Dr. Goldberg added that proposals for the 3 VA RFAs were still being accepted and could receive funding in FY2010.

Dr. Steele and Chairman Binns reasserted their concerns about the $11 million allotment, and Chairman Binns added that part of the objection stemmed from the history of overspending on neuroimaging. He recalled that the Committee had a similar reaction in 2004 when then Secretary Principi decided to spend $20 million per year on Gulf War illness research, and ORD spent $5 million on imaging equipment for research being conducted in San Francisco. Dr. Kupersmith replied by stating that he still defended

ORD's decision to fund the equipment, but that he could understand Chairman Binns' concern. Dr. Golomb expressed interest in seeing what percentage of the research carried out with the new imaging equipment would be related to Gulf War illness.

Dr. Steele then reiterated her concerns about the processes used to assign VA funding, and the VA's perceived need to quickly spend the money that would have gone to Dr. Haley had his contract not been cancelled. Dr. Kupersmith replied that all funding other than equipment spending and some administrative and hiring spending undergoes peer review prior to ORD approval. Dr. Goldberg then clarified that ORD did not go out looking for a way to spend a certain amount of money in a constrained amount of time. He stated that the equipment request from Dr. Weiner had been straightforward and carefully reviewed by the VA. Dr. Goldberg emphasized that the spending was approved because Dr. Weiner's need for equipment was perceived to be justified, not because the request focused on Gulf War research. Dr. Kupersmith added that the request had been submitted a while ago, and that he hoped the focus could turn to assessing what had been and would be accomplished over a period of several years, rather than how much money had been spent.

Dr. Sullivan then asked if another round of RFAs would come out in 2010. Dr. Goldberg replied that the plan involves RFAs being released every 6 months. Dr. Sullivan asked if they would be reviewed within the current fiscal year. Dr. Goldberg said he would have to double check, but that it was not likely. He added that RFAs would continue to be reissued every 6 months for the foreseeable future. Dr. Sullivan asked if there would be any limitations on investigators resubmitting proposals after being turned down for funding. Dr. Kupersmith said that this was an issue that NIH was looking into. Dr. Sullivan emphasized the importance of feedback being provided to investigators whose proposals were not approved. Dr. Kupersmith acknowledged the importance of this communication, and asked that Dr. Sullivan or others provide input to improve the process.

Dr. Kupersmith then expressed his belief that the Task Force report would do a lot to legitimize and destigmatize Gulf War illness within the medical community. Dr. Goldberg also commented on the incentive associated with the $250,000 per year budget for Gulf War research proposals. Dr. Kupersmith acknowledged the value of considering other forms of incentives to draw in new investigators to the Gulf War research field.

Mr. Hardie then remarked that he has been impressed with VA's suicide prevention outreach and employment at the VA. He added that he believes Dr. Kupersmith has a unique opportunity to draw in new scientists to the field by including language on the funding opportunities and recruitment of new Gulf War researchers in the press release that will accompany the Task Force report release.

Dr. Lange then applauded the ORD's efforts to increase Gulf War research funding and stated that she was optimistic about the allure of Gulf War research among members of the research community. She added that one of the largest challenges facing researchers drafting proposals was the design of strong subject recruitment strategies. Dr. Lange

recommended working with VSOs to encourage face-to-face interaction between researchers and veterans. Dr. Kupersmith replied that this approach was part of the strategy for the national cohort being developed under the CSP. Dr. Lange, who has experience conducting neuroimaging research, then commented on the great need for research focused on integrative physiology to be funded (in addition to neuroimaging equipment and research).

Dr. Ashford supported Dr. Lange's comment about the need for appropriate recruitment of veterans for clinical research. He stated that each VA hospital in the country should have a champion for Gulf War illness who could be the link between ill veterans seeking care and the physicians and researchers at WRIISCs and elsewhere. Dr. Kupersmith supported this type of approach.

Maj. Nichols suggested that the VA organize an open discussion on the "new field of Gulf War illness" in which ill Gulf War veterans, researchers and physicians sit down in the presence of various media outlets in order to destigmatize the illness. Maj. Nichols also expressed her belief that the MRI equipment be divided among other funding categories since it would ultimately be used by researchers within and outside of the Gulf War research field. Dr. Kupersmith agreed that it would be better to list only a percentage of the total equipment cost as "Gulf War research" funding.

Chairman Binns seconded Maj. Nichols' request that the VA think big about how to publicize Gulf War research. He commented on the enormous effort involved in recruiting veterans, and the advantage that media could play in leveraging recruitment power.

Dr. Sullivan expressed agreement with Dr. Lange regarding the importance of forging respectful relationships with veterans when recruiting them for research studies. Dr. Kupersmith acknowledged this essential approach, and remarked that one crucial piece is to share the results of the research with the veterans.

Chairman Binns thanked Dr. Kupersmith for sitting down with the Committee, adding that some of the concerns expressed by the veterans and Committee members might have been alleviated if the right proportion of the equipment funding had been allocated to the Gulf War research category. Dr. Kupersmith agreed and thanked the Committee for the discussion.

Chairman Binns then announced the next speaker, Mr. Steve Smithson.

Advisory Committee on Gulf War Veterans: Final Report Recommendations

Mr. Steve Smithson, Research Advisory Committee on Gulf War Veterans' Illnesses

Mr. Smithson presented a summary of the final findings and recommendations of the Advisory Committee on Gulf War Veterans (Appendix A – Presentation 9). The major issues on which the Advisory Committee made recommendations in this report included health care priority for Gulf War I veterans, access to and quality of care for Gulf War I

veterans, undiagnosed illnesses, identification of Gulf War I veterans in VA records, outreach and timeliness of communications. Mr. Smithson noted that there was only one dissenting (non-unanimous) vote cast when the Advisory Committee voted on the recommendations, and this point of contention involved disagreement over the recommendation to include Gulf War I veterans in the Post Deployment Integrated Care Initiative (PDICI) or expand the services of Environmental Agents to include services provided through PDICI. At the conclusion of the presentation Mr. Smithson remarked that the Task Force would be considering the recommendations as they moved forward.

Dr. Goldberg commented that the Task Force report would include a table summarizing what actions were taken for each of the recommendations made by the Advisory Committee.

Chairman Binns then clarified that the one issue of contention regarding PDICI involved disagreement over whether clinical care should be conducted within deployment health clinics (which also receive OEF/OIF veterans and therefore focus on PTSD and TBI) versus utilizing the Environmental Agents Service's group (which would be more focused on environmental exposures).

Dr. Lange said that she was surprised to learn that there had been dissension on this point because she perceived PDICIs to be the frontline primary care providers through which veterans enter the system and can then be referred to the WRIISCs and the Environmental Agents Service. Mr. Smithson said he had looked through the report and accompanying letter from the Advisory Committee but that no mention of these specific concerns was made.

Dr. Ashford commented that the PDICI has its own focus, and that it would therefore be wise to have a Gulf War specialist at each site.

Chairman Binns then asked if Mr. Smithson had any personal reaction to the Advisory Committee's recommendations. Mr. Smithson replied that his expertise is in benefits, and that he strongly agreed with extending the undiagnosed illness end date, but that he didn't think the report went far enough in addressing the problems with the undiagnosed illness issue or the issues with the IOM reporting process regarding presumptive disabilities.

Dr. Goldberg commented that the Task Force report would not mark the end of the process, and that the review would be ongoing. As such, Dr. Goldberg stated that some issues might not be addressed in the first Task Force report, but that did not preclude them from being addressed in future reports.

Mr. Hardie thanked Dr. Goldberg for his continued commitment to ill Gulf War veterans. Dr. Goldberg then remarked that Mr. Gingrich chose to lead the Gulf War Task Force because of his personal sense of responsibility to the veterans. Chairman Binns then expressed appreciation for the new standards being set for how the VA and government will handle exposure-related health problems in the future. Dr. Goldberg reassured the

Committee and the veterans in attendance that the report's focus was on Gulf War I veterans.

Chairman Binns then called for public comments.

Public Comments

Maj. Nichols spoke on behalf of the veterans who are upset about the ongoing legal dispute over the funding for Dr. Haley's research, and expressed her concern about the implications this may have for future research recruitment efforts among the Gulf War veteran community.

Mr. Robinson then expressed interest in hearing of any diagnostic trends being seen in Gulf War veterans who are being evaluated at the WRIISCs. Commenting on the challenge of recruitment, he added that about 12,000 veterans with undiagnosed illness claims were denied, and that these individuals might be willing to return if given the information about the VA's new attitudes toward Gulf War illness and undiagnosed illnesses.

Dr. Goldberg responded to this suggestion by explaining that although the VA did not have the authority to simply readjudicate claims once all the new rules get approved, records would be reviewed and letters sent to veterans whose previously rejected claims might qualify under the new rules. Mr. Smithson welcomed this unprecedented change whereby VA would be spearheading outreach.

Paul Sullivan, Executive Director of Veterans for Common Sense, then called in through an audience member's phone to make several comments which he later submitted via writing due to poor audio quality (see Appendix D).

Chairman Binns then thanked everyone for attending and adjourned the meeting.

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