Research Advisory Committee on Gulf War Veterans' Illnesses

November 2-3, 2009, 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 November 2-3, 2009 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
Carrolee Barlow*
Floyd Bloom
Beatrice Golomb*
Anthony Hardie
Marguerite Knox
William Meggs
James O'Callaghan
Adam Such

Consultant to the Committee
Jack Melling

Committee Staff
Kimberly Sullivan
Sadie Richards

Designated Federal Officer
Bill Goldberg

Other Members of the VA
John Gingrich, VA Chief of Staff
Joel Kupersmith, VA Chief Research and Development Officer
Timothy O'Leary, Dir. of Clinical Science R & D, Veterans' Health Administration

Guest Speakers
Mohammad Amin
Peter Dorsher
Clement Furlong
Robert Haley
Freya Kamel
Oksana Lockridge
Rosemary Toomey

* participated only on November 3, 2009, by phone

ABBREVIATIONS

AchE – Acetylcholinesterase

ADHD – Attention Deficit Hyperactivity Disorder

AHS – Agricultural Health Study

ALS – Amyotrophic Lateral Sclerosis

ANS – Autonomic Nervous System

CMI – Chronic Multisymptom Illness

CPAP – Continuous Positive Airway Pressure

CRADO – Chief Research and Development Officer

CSF – Cerebrospinal Fluid

CSP – Cooperative Studies Program

DoD – Department of Defense

FAME – Farming and Movement Evaluation

FDA – Food and Drug Administration

fMRI – functional Magnetic Resonance Imaging

GWI – Gulf War Illness

IRB – Institutional Review Board

IT – Internet Technology

MCS – Multiple Chemical Sensitivity

MRS – Magnetic Resonance Spectroscopy

NIEHS – National Institute of Environmental Health Sciences

NIH – National Institutes of Health

NGWRC – National Gulf War Resource Center

NTE – Neuropathy Target Esterase

OP – Organophosphate

PAC – Presidential Advisory Committee

PB – Pyridostigmine Bromide

PD – Parkinson's Disease

PON1 – Paraoxonase

PTSD – Post-Traumatic Stress Disorder

SD – Standard Deviation

SSRI – Selective Serotonin Reuptake Inhibitor

TBI – Traumatic Brain Injury

UARS – Upper Airway Resistance Syndrome

VA – Department of Veterans Affairs

VHA – Veterans Health Administration

WRIISC – War-Related Illness and Injury Study Center

Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses
November 2-3rd, 2009

Veterans Administration, 810 Vermont Avenue, Washington, DC

Agenda
Monday, November 2, 2009

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	**Neuropsychological profiles in toxicant-induced encephalopathies**	**Dr. Roberta F. White** **Res Adv Cmte Gulf War Illnesses**
9:30 – 10:15	**Neuropsychological functioning in the VA national health survey of Gulf War veterans**	**Dr. Rosemary Toomey** **Boston University**
10:15 – 10:30	**Break**	
10:30 – 11:15	**Chronic health effects from pesticides: results from the Agricultural Health Study**	**Dr. Freya Kamel** **National Institute of Environmental Health Studies (NIEHS)**
11:15 – 12:00	**Organophosphate mechanism of action and potential biomarker studies**	**Dr. Oksana Lockridge** **University of Nebraska**
12:00 – 12:45	**Genetic variability and sensitivity to organophosphate exposures**	**Dr. Clement Furlong** **University of Washington**
12:45 - 1:45	**Lunch**	
1:45 - 2:30	**UTSW preclinical studies preliminary results**	**Dr. Robert Haley** **University of Texas Southwestern** **VA Dallas Healthcare System**
2:30 – 3:00	**Committee discussion on neurotoxicant biomarkers**	**Dr. James O'Callaghan** **Res Adv Cmte Gulf War Illnesses**
3:00 – 3:15	**Break**	
3:15 - 4:00	**Fibromyalgia & GWI: Treatments using laser stimulation of the ANS**	**Dr. Peter Dorsher** **Mayo Clinic Jacksonville**
4:00 – 4:45	**Effect of CPAP on Gulf War Illness Symptoms**	**Dr. Mohammad Amin** **Northport VAMC**
4:45 – 5:15	**Public Comment**	

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

Tuesday, November 3, 2009

8:00 – 8:30	**Informal gathering, coffee**	
8:30 – 10:00	**Future VA Gulf War research**	**Dr. Joel Kupersmith** **Chief Research and Development Officer** **Dept. of Veterans Affairs** **and Committee discussion**
10:00 – 11:00	**VA Briefing**	**Mr. John Gingrich, Chief of Staff**
11:00 – 11:15	**Break**	
11:15 – 11:45	**Continuation of VA research discussion**	
11:45 – 1:00	**Committee business; planning for 2010**	**Mr. Jim Binns and** **Committee discussion**
1:00 – 1:30	**Public Comment**	
1:30	**Adjourn**	

DAY 1

The November 2-3, 2009 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

Chairman Binns called the meeting to order at 8:30am. He then outlined revisions made to the meeting agenda before introducing Dr. Roberta White, the Committee's Scientific Director and first speaker of the day.

Neuropsychological Profiles in Toxicant-Induced Encephalopathies

Dr. Roberta White, Committee Scientific Director

Dr. White, who has 30 years experience evaluating individuals exposed to various neurotoxicants, provided an introductory presentation on toxicant-induced encephalopathies from a neuropsychological perspective (See Appendix – Presentation 1). She first spoke about the classification system that she devised in the 1980s to identify characteristic exposure types and clinical outcomes. She described severe toxic encephalopathy outcomes as well as the less severe subclinical encephalopathy. Dr. White then presented a summary of the clinical research and literature findings on populations exposed to insecticides such as organophosphates (OPs) and other pesticides considered acetylcholinesterase (AChE) inhibitors that were widely used during the time of the Gulf War.

Dr. White remarked that mood change is the most consistent finding in populations exposed to these neurotoxicants. She stated that mood findings can be a symptom of brain damage and not a comorbid condition, and that mood should therefore not be controlled for in studies of chemically exposed populations. Other common symptoms she reported related to these exposures include: fine manual motor impairment, visuospatial tasks, difficulty retrieving visual memories, executive system and attention deficits. Dr. White has also seen Parkinsonian syndromes in some exposed individuals. She concluded her presentation by discussing issues related to clinical diagnosis and the level of neuropsychological dysfunction required to diagnose a deficit.

Dr. Bill Meggs, a member of the Committee, asked Dr. White to comment on the validity of neuropsychological testing in toxicological cases in light of a study of toluene abusers published in Clinical Toxicology which found that imaging results accurately predicted dose-response effects but that neuropsychological abnormalities did not. Dr. White responded that her neuroimaging studies have found that the dose-effect relationships appear to be stronger with neuropsychological tests than with neuroimaging, depending on the imaging technique used. She added that some new magnetic resonance spectroscopy (MRS) and functional magnetic resonance imaging (fMRI) imaging techniques may reveal strong dose-response effects, but that these methods are still in the

experimental stages and are not currently legitimate for diagnosis. Dr. White emphasized the importance of selecting appropriate neuropsychological tests for research studies as all tests do not provide the same sensitivity levels, and called for further exploration of the relationships between imaging and behavioral outcomes.

Within the context of Gulf War Illness (GWI), Dr. Jack Melling, consultant to the Committee, asked whether patients are presenting mainly because of known exposure to some specific agent or if certain symptoms prompt veterans to seek care. Dr. White replied that both circumstances apply to patients with GWI.

Dr. Jim O'Callaghan, a member of the Committee, asked if Dr. White has encountered cases of Parkinson's Disease in Gulf War (GW) veterans, and whether neuropsychological tests might be useful in diagnosis.

Dr. White replied that she has not conducted longitudinal, prospective research on Parkinson's patients, though she has seen patients with chemical exposures who developed Parkinsonian syndromes on a delayed basis. She remarked that in some patients she has studied prospectively (e.g. those with Huntington's Disease) neuropsychological deficits appear before neuroimaging deficits are detectable. Dr. White also said that she is very interested in the relationship between aging, neurodegenerative diseases and chemical exposures.

Mr. Jim Bunker, a Gulf War veteran and president of the National Gulf War Resource Center (NGWRC), asked if Dr. White had ever considered assessing individual deficits/declines in functioning by re-testing veterans with the qualifying exam they each took when entering the armed services. Dr. White said that she had re-administered these tests to veterans when working at the Environmental Hazards Center, but that she had not been granted access to their initial results for comparison. Mr. Bunker encouraged revisiting the study, and Dr. White said that she had data for 300 veterans that could be revisited.

Maj. Denise Nichols remarked that she and other veterans who were highly capable of multi-tasking prior to their chemical exposures had experienced significant declines in executive functioning after the Gulf War. Dr. White replied that this didn't surprise her, since executive functioning is the common pathway for any kind of brain damage.

Dr. Freya Kamel, a staff scientist at the National Institute of Environmental Health Sciences (NIEHS), asked if Dr. White has had the opportunity to follow people over time to determine whether various non-specific systems tend to progress to more overt dysfunction. Dr. White replied that she has followed a number of people longitudinally (both in terms of neuropsychological functioning and symptom complaints), and that age has not majorly impacted most of these individuals yet. Many of these people had not reached their 50s or 60s at most recent follow-up, so Dr. White felt that further longitudinal testing is important because this may be a very valid concern.

Dr. Peter Dorsher, Chairman of Physical Medicine and Rehabilitation at the Mayo Clinic in Florida, asked Dr. White if deterioration of neuropsychological functioning associated with chemical exposures could be mitigated in any way. Dr. White replied that it would be very difficult to repair the brain long after it has been damaged in this way (e.g. by acetylcholinesterase inhibitors).

Mr. Anthony Hardie, a member of the Committee, thanked Dr. White for her presentation, noting that it mirrored his experiences as an ill Gulf War veteran. He also commented that military enlistees in the early 1990s (i.e. Gulf War veterans) were high functioning individuals, nearly all of whom were high school graduates. Mr. Hardie also praised the new standards put out by the federal VA for service connection related to traumatic brain injury (TBI). He encouraged the VA to extend these types of standards to veterans suffering from GWI. Dr. White then expressed her concern that the brains of many military recruits are still forming when they go into combat, which may influence the permanence of the consequences of various service-related exposures. Dr. White also stated that she is interested in the role of gene-environment interactions as they relate to GWI.

Dr. Meggs remarked that many of the neuropsychologically impaired individuals exposed to toluene experience fluctuating deficits that wax and wane, and often become more severe following subsequent exposures to solvents. He asked if Dr. White had any thoughts on the validity or mechanism of these reports. Dr. White replied that all individuals with brain damage will experience fluctuations in the severity of their symptoms. She remarked that very few of the Gulf War veterans she has seen have been diagnosed with Multiple Chemical Sensitivity (MCS), but that many reported being more bothered by chemicals after their exposure to the Gulf War theater.

Chairman Binns then thanked Dr. White for her presentation before Dr. Kimberly Sullivan, Scientific Coordinator for the Committee, introduced the next speaker.

Neuropsychological Functioning in the VA National Health Survey of Gulf War Veterans

Dr. Rosemary Toomey, Boston University

In her presentation, Dr. Toomey discussed the results of a neuropsychological study she conducted in 1,061 deployed and 2,883 non-deployed veterans 10 years after the Gulf War (See Appendix – Presentation 2). The eight neuropsychological domains or factors assessed were verbal memory, attention/working memory, visual memory, executive functioning, perceptual motor speed, visual organization, motor speed, and sustained attention. Using a cutoff score of minus 2 standard deviations (SD), motor speed and sustained attention were significantly worse in deployed versus non-deployed GW veterans in her study. Dr. Toomey reported that studying the groups by deployment status only (deployed vs. non-deployed) irrespective of GWI status, may have obscured some interesting findings within subgroups of ill deployed veterans. For example, 4 of the 27 individual test variables included within the 8 cognitive factor domains analyzed were

significantly impaired in deployed Gulf War veterans compared to non-deployed GW veterans.

Dr. Toomey also looked at whether exposures to various independent exposure variables (e.g. Khamisiyah plume, pesticides, pyridostigmine bromide) were correlated with impairment of each of the 8 neuropsychological factor domains. She reported that Khamisiyah exposure was significantly associated with reduced motor speed in exposed GW veterans versus non-exposed veterans. Self-reported exposures to pesticides, nerve gas, SCUD missiles, pyridostigmine bromide pills, and contaminated food or water were also associated with significant reductions in sustained attention.

Dr. Toomey also addressed deficit measurement issues that arose in this study. She expressed concern with methods used to identify cognitive deficits, noting that a high-functioning individual who experienced significant cognitive impairment might not be identified as suffering from a deficit if the individual's post-exposure functioning still falls within the range considered "normal" or "low normal" for the population at large.

Dr. White commented that she has never found anything significant when making large group comparisons. Dr. White also thought it was interesting that all of the positive neuropsychological outcomes had working memory components. She strongly approved of Dr. Toomey's use of a measure to control for veterans' pre-existing differences in cognitive abilities. Dr. White was also interested in Dr. Toomey's self-reported exposure data, and was intrigued by the finding that self-reported SCUD missile exposure was significantly associated with perceptual motor speed impairment.

Dr. White then asked if Dr. Toomey plans to run future analyses using days of self-reported exposure as a proxy for exposure dose. Dr. Toomey replied that she thought it would be a good idea. Dr. White commented that, like Dr. Toomey, she had found a correlation between verbal memory impairment and Khamisiyah exposure in one of her studies of Gulf War veterans. Speaking again from her own research experience, Dr. White remarked that looking at just the *severe* chronic multisymptom illness (CMI) cases might reveal some interesting findings.

Dr. Sullivan thanked Dr. Toomey for the work she put into her study, particularly with regard to recruiting a very large, and therefore statistically powerful, group of veteran participants. She also commented that it would be very useful if Dr. Toomey could analyze her data according to the exposure amounts or durations that veterans had to various agents, particularly with regard to pyridostigmine bromide (PB) pills. Dr. Sullivan also asked how exposure to nerve agents at Khamisiyah was determined in Dr. Toomey's study. Dr. Toomey replied that the plume model was used, and that it was not self-reported data of exposure.

Dr. Meggs commented that he was impressed by Dr. Toomey's research findings.

LTC Marguerite Knox, a member of the Committee, asked if stimulants could be used to treat veterans with memory or attention deficits. She also asked if research demonstrating

that stroke victims with brain damage often rebuild connections in other parts of the brain allowing for compensatory executive functioning holds relevance for cognitively impaired Gulf War veterans. She concluded her question by asking Dr. Toomey what her goals were for the patients she sees.

Dr. Toomey replied that the patients she sees are not all Gulf War veterans, and that stimulants have not often been used to treat impairments other than attention deficit hyperactivity disorder (ADHD) and, in a few cases, dyslexia. Dr. Toomey remarked that stimulant drugs were not as effective in remedying the organizational and executive multi-tasking deficits (as opposed to attentional components) associated with ADHD. She believes that more environmental treatment interventions are needed to address these types of deficits.

Dr. Meggs commented on the plasticity of the human brain, and asked if any exercises existed that could boost ill veterans' executive functioning. Dr. Toomey replied that the field of cognitive rehabilitation could be explored in order to identify helpful treatment interventions. She mentioned that she had used cognitive rehabilitation exercises with patients suffering from schizophrenia spectrum disorders, where cognitive deficits can be profound. Dr. Toomey also felt that some patients might also be able to use their individual cognitive strengths to compensate for their cognitive weaknesses.

Dr. White commented that a subset of patients suffering from stroke seem to benefit from stimulants, but that this likely has more to do with increased arousal and willingness to do things. She also noted that selective serotonin reuptake inhibitors (SSRIs) sometimes work for these individuals. Dr. White emphasized that the recovery of executive functioning following stroke is not complete, and that cognitive functioning often fluctuates from day-to-day in these individuals.

Dr. Mohammad Amin, a physician specializing in sleep disordered breathing at Stony Brook University and the Northport VAMC, asked if Dr. Toomey ever refers her patients that present with cognitive dysfunction and attention deficit disorders for sleep studies. Dr. Toomey replied that she screens all of her patients for sleep disorders as part of her clinical history review.

At 10:15am Chairman Binns thanked Dr. Toomey for her presentation and called for a 15 minute break.

After reconvening from the break, Dr. Sullivan introduced the next speaker.

Chronic Neurologic Effects of Pesticides: Results from the Agricultural Health Study

Dr. Freya Kamel, National Institute of Environmental Health Sciences at NIH

Dr. Kamel discussed the findings of the Agricultural Health Study (AHS), which involved assessing 57,000 pesticide applicators and their spouses for levels of pesticide exposure and neurologic dysfunction and disease, among other outcomes (see Appendix – Presentation 3). This study relied on self-reported data, but Dr. Kamel noted that she has conducted biomarker studies which have validated this study's questionnaire data. The study revealed that participants with a cumulative lifetime use of insecticides had an increased risk of experiencing 10 or more neurologic symptoms in the year prior to study enrollment. Of the various classes of pesticides and herbicides studied, strong and consistent effects were found for organophosphates and organochlorines (insecticides commonly used during the GW). Accounting for recent pesticide use did not change association with cumulative use. Importantly, effects were present in applicators with no history of pesticide poisoning or high exposure events but rather chronic cumulative exposures. Dr. Kamel then stated that use of high exposure application methods were also associated with increased health symptom risk. Dr. Kamel also touched on her research findings that pesticide applicators exposed to fungicides, organophosphates, organochlorines or carbamates were at increased risk for retinal or macular degeneration. A follow-up, prospective study of the applicators and their spouses has revealed some intriguing preliminary results. Dr. Kamel also discussed her ongoing study of Parkinson's Disease (PD) in pesticide applicators, as well as some research she is conducting on veterans with Amyotrophic Lateral Sclerosis (ALS) and lead exposure.

Dr. Meggs asked if Dr. Kamel looked at individual symptoms, rather than just clustering participants into groups based on the number of symptoms they had experienced. Dr. Kamel replied that her research group looked at 23 symptoms, grouped a priori into several functional domains. She remarked that factor analysis wasn't very fruitful. She admitted that her results could indicate actual increased symptomology, but could possibly be partly attributed to recall bias. She stated that some neurobehavioral testing is currently being done on 700 individuals from the AHS, and that comparison of these results to the questionnaire findings will provide further insight.

Dr. Oksana Lockridge, a biochemist from the University of Nebraska Medical Center, then asked if age of onset for macular degeneration was earlier in the pesticide applicators than would normally be expected. Dr. Kamel replied that she did not look at that with respect to macular degeneration, but that all of the analyses in her studies controlled for age. The macular degeneration studies were restricted to individuals over age 50, then adjusted for age. She believed the results seen are independent of age. In the PD studies, age of onset was not affected by pesticide exposure.

Dr. Robert Haley, an epidemiologist at UT Southwestern Medical Center, asked what multivaried analysis reveals when exposure to organochlorines vs. organophosphates is controlled. Dr. Kamel replied that controlling for exposure to organophosphates or organochlorines does not impact the findings. She therefore cautioned against focusing

only on organophosphates, though she acknowledged that the OP chemicals were more relevant to the Gulf War veterans than organochlorines.

Dr. White mentioned that Dr. Rick Myers from Boston University found an earlier age of PD onset in a sibling cohort study published in Neurology a few years ago. Dr. Kamel said that she had not seen that in her research, but noted that her study is fairly small and that the PD cohort may grow as AHS participants age. She suggested that this could lead to greater statistical power for analyses. Dr. White followed up by asking if Dr. Kamel has any data on dopamine treatment response. Dr. Kamel replied that the Farming and Movement Evaluation (FAME) follow-up study only includes participants who have responded to dopamine treatment.

Chairman Binns asked Dr. Kamel if it had been solidly determined that organophosphates and their metabolites are not retained in the body. Dr. Kamel replied that this was not her area of expertise, but that she was not aware of any OPs that would exist in the body for more than a day or two. Dr. Lockridge remarked that the fat-soluble OPs can re-poison individuals after initial poisoning because of their slow release from fatty tissue, but she believed no OPs would stay in the body more than a few weeks. Dr. Haley agreed. Dr. Clement Furlong, a biochemist at the University of Washington, stated that although an OP and its metabolites clear the body rapidly that the proteins to which it may have bound can remain altered for up to about 33 days. He further stated that this was dependent on the half-life of the specific OP and the site of the protein in the body.

Chairman Binns then thanked Dr. Kamel for her presentation before Dr. Sullivan introduced the next speaker.

Organophosphate Mechanism of Action and Potential Biomarker Studies

Dr. Oksana Lockridge, University of Nebraska Medical Center

Dr. Lockridge described research findings from her investigation of mechanisms that might be responsible for low dose organophosphate (OP) toxicity (See Appendix – Presentation 4). Her research recently identified a new binding site (tyrosine) by which OPs can attach to and modify proteins that have no active site serine. These findings came from studies in mice, mouse tissue and human plasma. The identification of this new binding motif is significant because it indicates that the mechanism underlying OP toxicity could involve additional proteins which were formerly not thought to be involved and are more far reaching than the acetylcholinesterase neurotransmitter system. Dr. Lockridge then gave an overview of her research into whether tubulin could be involved in OP neurotoxicity. She showed slides of thinned microtubules from mouse neurons that had been exposed to OPs to illustrate her findings and to suggest that OP-induced damage to the microtubules could result in cognitive deficits including slowed processing speeds. She concluded by describing the research she is conducting that involves making and using antibodies to identify OP-labeled proteins. Based on the research she has conducted thus far using antibodies to soman-labeled tyrosine, Dr. Lockridge believes this approach may eventually be used to diagnose low-dose OP exposure in humans using hand-held devices in the field including in occupational, home and battlefield settings.

Dr. Bloom, a member of the Committee, asked Dr. Lockridge if she had run any in vitro tests using tyrosine kinase receptors, which are important to intra- and intercellular signaling. Dr. Lockridge replied that she had not yet done so, but asked where she could obtain them for her research. Dr. Bloom replied that many chemical supply companies sell these, Sigma Chemicals being one.

Dr. Furlong asked Dr. Lockridge if she had given any thought to how tubulin modification ties in to neuropathy target esterase (NTE) modification and the requirement for aging of that adduct to generate paralysis. Dr. Lockridge replied that tyrosine adducts don't age. Dr. Furlong agreed, noting that there must be interplay between tyrosine and NTE because both are involved in transport down the neuron. Dr. Lockridge said she did not know what interactions might exist between the two.

Dr. Meggs asked Dr. Lockridge to explain the "aging" process, and she gave a brief biochemical description of this chemical reaction. Dr. Lockridge explained that aging is a specific chemical process involving the loss of an alkyl group via an enzyme-catalyzed reaction which does not occur in tyrosine-labeled phosphates.

Dr. Kamel then asked if Dr. Lockridge thought the OPs bind to dopamine, and if an antibody could be generated to recognize that. Dr. Lockridge asked how large dopamine was. Dr. Kamel replied that it was about the size of an amino acid, similar in size to tyrosine, from which it's made. Dr. Lockridge didn't know that tyrosine is metabolized into dopamine. Dr. Kamel explained that she asked the question because dopamine is what's lost in Parkinson's Disease. Dr. Lockridge thought targeting the synthesis of dopamine would be most promising since dopamine's turnover is so fast.

Chairman Binns asked Dr. Lockridge what she felt was the significance of her findings for Gulf War veterans in terms of biomarkers that might still be detected. Dr. Lockridge replied that she didn't believe OP-modified proteins could be detected this far after exposure (18+ years). She did remark that the existence of some life-long consequences of OP exposure indicated that some biological changes such as perhaps NTE should still be detectable.

Dr. Furlong followed up by asking if any post-exposure blood samples were taken from the veterans within a reasonable time of detection that still exist in freezers today. Dr. Lockridge and Dr. Sullivan replied that such samples do exist. Dr. Lockridge added that obtaining access to them would be very difficult. Dr. Furlong replied that he felt doing so would be very important.

Dr. Meggs asked if oximes have any effect at the serine binding site. Dr. Lockridge replied that the oximes do not have any effect on OP tyrosines, according to a recent study conducted in the UK by a group of researchers at Porton Down.

Chairman Binns then thanked Dr. Lockridge for her presentation, and Dr. Sullivan introduced the next speaker.

Genetic Variability and Sensitivity to Organophosphate Exposures

Dr. Clement Furlong, University of Washington

Dr. Furlong spoke of what has been learned about OP exposures and the consequences of genetic variability in modulating mixed exposures (See Appendix – Presentation 5). One topic discussed in detail was the role that plasma paraoxonase (PON1) plays in detoxifying organophosphorus insecticides and their metabolites (namely diazoxon and chlorpyrifos oxon). These OP insecticides were used widely during the Gulf War. After providing a brief historical background, Dr. Furlong discussed the implications of genetic and developmental variability in different individuals' plasma PON1 levels. He emphasized that gene/protein-environment interactions are very important in modulating the consequences of OP exposures. Dr. Furlong also gave an overview of the processes by which his lab is researching protein adducts as biomarkers of OP exposure. Dr. Furlong explained that protein adducts are proteins whose active sites are covalently attached to organophosphate inhibitors, and thus they have much longer half-lives (e.g., 11-33 days) than free metabolites in urine or plasma. Thus, protein adducts offer a much broader window in time for assessing exposures. Dr. Furlong added that analysis of these modified "biomarker proteins" by mass spectrometry provides a highly sensitive approach for documenting and quantifying exposures.

Dr. Nancy Klimas, an immunologist and physician at the University of Miami and the Miami VA Medical Center, asked if ritonavir would be helpful in acute OP poisoning cases. Dr. Furlong replied that this type of approach could be useful, and that his lab has been developing recombinant, injectable PON1 for this purpose.

Dr. Sullivan asked Dr. Furlong to elaborate about the increased risks associated with exposures to mixtures of OPs. Dr. Furlong replied that exposure to one toxic compound capable of inhibiting carboxyl esterase (a liver enzyme responsible for metabolizing many compounds to which an individual is exposed) can max out the body's ability to metabolize other compounds, including those normally considered safe for human exposure (e.g. pyrethroids). Therefore, if an individual is concurrently exposed to multiple OPs, chemicals that might not do any damage on their own can potentiate the toxic effects of others. Dr. Sullivan remarked on the significance of this phenomenon in the context of the Gulf War, where veterans were exposed to 15 different pesticides with 12 different active ingredients. Dr. Furlong replied that individuals with bad PON1 status (due to genetic predisposition) who were exposed to a combination of pesticides would be at a greater risk for long-term health consequences due to their impaired ability to metabolize certain toxins.

Chairman Binns asked Dr. Furlong to repeat his comments regarding GWI and mitochondrial functioning. Dr. Furlong replied that some individuals with mutations affecting mitochondrial functioning experienced a decreased ability to modulate oxidative stress. Chairman Binns asked if something that would affect the ability to handle oxidative stress could potentially make a difference in patients with these problems. Dr. Furlong confirmed that such treatments might be possible, and remarked

on one current clinical trial using coenzyme Q10 to enhance an individual's ability to modulate oxidative stress. He also emphasized the promise of early detection and intervention to prevent or delay the onset of symptoms in individuals with these types of genetic mutations.

Chairman Binns then asked Dr. Furlong what other implications he saw for biomarkers or treatments that would apply to Gulf War veterans exposed during the war. Dr. Furlong said that he has given a lot of thought to the issue but he has not come up with any viable solutions.

Dr. Meggs asked if Dr. Furlong had any thoughts about prophylaxis that could be given in place of PB to troops facing potential nerve gas exposure. Dr. Furlong said that one of his major current endeavors involves engineering PON1 to better hydrolyze nerve agents, so that it could be injected in the event of exposure.

Chairman Binns adjourned the meeting for lunch at 12:49pm. The meeting reconvened at 1:45pm, when Dr. Sullivan introduced the next speaker.

Highlights of the Initial Feasibility Year of the Preclinical Studies

Dr. Robert Haley, UT Southwestern Medical Center

Dr. Haley presented recent findings from the ongoing preclinical animal studies his research group has been conducting to investigate and identify mechanisms of the chronic neurological effects of Gulf War chemicals, with the ultimate goal of developing treatments (See Appendix – Presentation 6). Dr. Haley first spoke about the development of mouse models of chronic neurotoxicity from chlorpyrifos and PB. He then provided an overview of preliminary findings in these mouse models related to memory circuits, autonomic nervous system functioning, dopamine turnover, and development of ALS and brain cancer. This was followed by a discussion with the Committee regarding these findings.

Committee Discussion on Neurotoxicant Biomarkers

Dr. Jim O'Callaghan, Committee Member

Dr. O'Callaghan initiated the discussion on the progression of biomarker research related to identifying mechanisms to explain Gulf War Illness.

Dr. Haley remarked that his preliminary preclinical studies have confirmed that PB appears to be a highly dangerous chemical which synergizes with chlorpyrifos to exert effects in mice and rats after chronic low-dose exposure. Dr. Haley also noted that chronic exposure to low doses of chlorpyrifos affected basal synaptic transmission in a region of the hippocampus (associated with memory and learning). Dr. Haley also found that chlorpyrifos and PB enhance autonomic activity acutely but impair it chronically in mice, particularly affecting the parasympathetic functions. In one ongoing study Dr. Haley also found an increased turnover of dopamine and serotonin in the mouse brain after exposure to chlorpyrifos and PB. Dr. Haley's research also found interesting results

regarding ALS and the growth of brain tumors in mice exposed chronically to low-dose mixtures of pesticides and PB. He concluded his presentation by discussing neuroinflammation, mitochondrial damage and intracellular phosphorylation as possible mechanisms of the effects observed in the animal model research.

Dr. Sullivan remarked that it would be helpful to have data on a greater number of pesticides that were used in the Gulf War (in addition to chlorpyrifos). Dr. Haley agreed to an extent, noting the difficulty of receiving funding for toxicological studies.

Dr. O'Callaghan commented that neuroinflammation played a prominent role in the preclinical study findings and he asked Dr. Haley if peripheral benzodiazepine receptor imaging had been conducted as planned. Dr. Haley said that the protocol had been completed but would not be receiving funding. Dr. O'Callaghan then asked if a study could be conducted in ill veterans that would involve priming them to have an inflammatory response prior to neuroimaging. Dr. Haley replied that he didn't believe such a neuroinflammatory challenge is needed. Dr. O'Callaghan clarified that he was suggesting this type of procedure as a possible clinical biomarker test that could be used in the absence of other evidence. Dr. Haley replied that caution is needed when conducting studies of Gulf War veterans, particularly with regard to screening out veterans who are ill due to other causes of disease and dysfunction.

Mr. Hardie thanked Dr. Haley for the research that his team has been doing, and expressed disappointment in the Department of Veterans Affairs' decision to cancel funding for Dr. Haley's research. Dr. Meggs followed up by stating that he hopes Dr. Haley will be able to continue his research.

Dr. Furlong recommended that Dr. Haley investigate the effects of oxidative stress by looking for disruption of mitochondrial function in the white cells of the brain and periphery in his mouse models.

Dr. Amin asked if increased levels of catecholamines affect heart rate variability and sympathetic nervous system signaling in patients with Gulf War Illness. Dr. Haley replied that evidence from some of his human and mouse model research suggests that parasympathetic impairment is characteristic of Gulf War Illness. He does not think that this abnormality necessarily indicates any abnormal sympathetic or catecholamine functioning. Dr. Amin replied that his research may suggest otherwise.

LTC Knox asked Dr. Haley if he felt enough evidence exists to warrant a recommendation be given to the Department of Defense (DoD) that troops no longer receive PB for prophylactic purposes. Dr. Haley was not aware that any troops were being given PB, but that he would support its use strictly in the event that troops were exposed to soman.

Chairman Binns thanked Dr. Haley for his presentation before calling for a 15 minute break. Before introducing the treatment-oriented speakers for the afternoon, Dr. Sullivan asked everyone to remember that the DoD had estimated that 41,000 Gulf War veterans

were likely overexposed to pesticides, and that another 100,000 were exposed to low-dose sarin during the Gulf War making the discussions today highly relevant to Gulf War veterans' health.

Fibromyalgia & Gulf War Illness: Treatment Using Laser Stimulation of the Autonomic Nervous System

Dr. Peter Dorsher, Mayo Clinic Florida

Dr. Dorsher spoke about fibromyalgia and GWI, focusing on autonomic nervous system (ANS) dysfunction and the neuroendocrine model of disease, prior to discussing the use of acupuncture to treat these diseases (see Appendix – Presentation 7). Dr. Dorsher discussed how various triggers, including chemical exposures, can act synergistically to throw the autonomic nervous system out of balance and contribute to neurologic dysfunction. Based on the outcome of studies in patients with fibromyalgia and musculoskeletal pain, Dr. Dorsher believes that laser acupuncture would be a reasonable and promising treatment to test in veterans with Gulf War Illness.

Dr. Meggs asked if the laser acupuncture that Dr. Dorsher advocates is similar to the cranial laser light treatments discussed by Dr. Margaret Naeser at the June 2009 Committee meeting. Dr. Dorsher replied that the laser treatments to the skull would also be affecting blood cells and mitochondrial functioning, in particular. Dr. Naeser, who was also in attendance at this meeting, commented that the goal of her laser therapy treatment is to stimulate the mitochondria to make ATP. She also remarked on the strong anti-inflammatory effects of laser acupuncture which could also prove helpful. Dr. Meggs asked if the hypothalamus was affected and Dr. Naeser replied that it could be through effects exerted on the cerebrospinal fluid (CSF).

Ms. Angela McLamb, an ill Gulf War veteran, then spoke briefly about the acupuncture treatment she received for 5 months following her return from the Gulf War, which she credited for relieving her from the numbness she had been experiencing in her arms and legs after her return from the war.

Chairman Binns asked if acupuncture could be used to modulate an overactive sympathetic ANS. Dr. Dorsher replied affirmatively, noting that the strength of acupuncture treatment lies in its ability to return the body to a state of homeostasis. Chairman Binns asked Dr. Dorsher if he saw improvements in symptoms other than pain. Dr. Dorsher replied that as the pain subsides, the paleocortical and neocortical activation diminishes. This is also associated with reduced depression, enhanced sense of well-being, decreased irritable bowel symptoms and other improvements in functioning that are interconnected aspects of the feedback loop that are also observed.

Chairman Binns thanked Dr. Dorsher, then Dr. Sullivan introduced the final speaker of the day.

Effect of CPAP on Gulf War Illness Symptoms

Mohammad Amin, Northpoint VAMC

Dr. Amin spoke about the role that sleep disordered breathing plays in what he described as functional somatic syndromes including Gulf War Illness (See Appendix – Presentation 8). Dr. Amin discussed studies that he has conducted in patients with fibromyalgia and GWI, including a pilot study in which he used continuous positive airway pressure (CPAP) in ill Gulf War veterans. The veterans who received CPAP reported decreased symptoms after 3 weeks of treatment when compared to veterans with GWI receiving sham treatment (a CPAP machine not delivering pressured air). Dr. Amin found that in ill Gulf War veterans receiving CPAP treatment improved symptomatology (self-reported pain, fatigue) was correlated with reduced shifting between sleep states. Dr. Amin then took some questions before discussing some detailed findings from his cross-sectional study.

Dr. Meggs asked what the anatomical origin for the upper airway resistance syndrome (UARS) is. Dr. Amin replied that it lies in the throat area (namely the nasal, oral or hypopharynx), and that UARS is typically characterized by hypertrophy of the mucosal cells lining the upper airway, often accompanied by post-nasal drip and congestion. Dr. Meggs confirmed that rhinitis is common among these patients.

Dr. Sullivan asked for clarification regarding the non-therapeutic CPAP (sham). Dr. Amin replied that the same noise is generated, but that no pressure reaches the mask.

Mr. Hardie asked for clarification regarding the distinction between the two types of sleep apnea – that with central nervous system origin versus anatomic sleep apnea. Dr. Amin replied that anatomical sleep apnea is associated with an effort to breathe, whereas sleep apnea with central nervous system origins is not. Mr. Hardie asked Dr. Amin if ill Gulf War veterans had more problems inhaling or exhaling. Dr. Amin replied that veterans with GWI primarily had trouble with inspiration during sleep. Mr. Hardie asked if Dr. Amin had any recommendations for ill Gulf War veterans such as himself who suffer from trouble exhaling. Dr. Amin did not have any specific recommendations for Mr. Hardie, though he noted that compromised exhalation generally indicates problems in the bronchial tree.

Chairman Binns asked Dr. Amin whether continued use of the CPAP machine would be necessary for ill Gulf War veterans to experience continued benefits. Dr. Amin replied that he expects continued use of the CPAP machine will be necessary.

Dr. Amin then concluded his presentation by presenting graphical images of the breathing patterns (pressure and flow) of ill Gulf War veterans compared to controls, followed by a discussion of an adaptive hypothesis to explain the presence of sleep stage shifts in ill Gulf War veterans.

At the conclusion of Dr. Amin's presentation, Dr. Sullivan asked if CPAP treatment might help improve the mitochondrial functioning that is thought to be a potential

problem in GW veterans. Dr. Amin replied that this was the question he was driving at when he asked Dr. Haley about increased levels of catecholamines and sympathetic nervous system functioning. In his current study of CPAP in ill Gulf War veterans Dr. Amin is only relieving pharyngeal collapse. He doubted that oxygenation of the blood was affected. Dr. Sullivan thanked Dr. Amin for his presentation, noting that many ill veterans she has encountered have complained of sleep problems.

Chairman Binns asked if every ill Gulf War veteran Dr. Amin had studied presented with sleep problems. Dr. Amin confirmed that all veterans with GWI that he has seen have exhibited air flow limitations during sleep, as determined by using a catheter in a sleep lab. Dr. Haley asked what the minimal setup would require in order to accurately measure pharyngeal dysfunction in veterans with GWI, remarking that one of his earlier studies did not catch significant differences in sleep disturbances between ill veterans and non-ill controls, even after 4 nights of observation in a sleep lab. Dr. Amin replied that his study used strict criteria to define GWI, and to exclude participants from the control cohort if they met any threshold criteria. He said that the essential test, called a polysomnogram, required participants to spend one night in a sleep lab during which the breathing effort would be measured with a pharyngeal catheter.

Chairman Binns asked Dr. Amin to clarify whether his findings indicate impairment of the autonomic nervous system in veterans with GWI. Dr. Amin replied that the ill veterans he has studied appear to have increased sympathetic tone.

Chairman Binns thanked Dr. Amin before inviting members of the audience to come forward with their questions.

Public Comments

Mr. Bunker spoke about a few concerns he had regarding the ongoing recruitment for several VA research studies. He first expressed concern over the exclusionary criteria preventing ill Gulf War veterans with post-traumatic stress disorder (PTSD) or depression from participating. He remarked that many veterans, in order to receive care for themselves and their families, were advised by their service officers to take these diagnoses since GWI was and is not considered for service-connection. He also took issue with the VA's stance on GWI as a psychiatric disorder. He noted that a report published in October 2008 by a working group convened by the National Center of Ethics and Health Care for the Veterans Health Administration found that veterans with PTSD could be used in research. He emphasized his belief that veterans with PTSD should be allowed to participate in any and all research. Mr. Bunker also stated that he supports Dr. Lea Steele's diagnostic criteria for GWI, and feels all researchers should use it in their studies of GWI. Mr. Bunker also emphasized his belief that GWI research should be focused on treatment.

Ms. Alison Johnson, Chair of the Chemical Sensitivity Foundation, said that she would provide complementary copies of her new book, *Amputated Lives: Coping with Chemical Sensitivity*, to any interested scientists. She also spoke about showing her film on Gulf

War Syndrome to the Northport VA in the spring, at which Dr. Gold asserted his belief that Gulf War Syndrome is not related to toxic exposures.

Maj. Denise Nichols, a Gulf War veteran and nurse, expressed concern with the lack of updates from the brain lab. She wanted to know if brain tissue samples are being collected from deceased veterans who suffered from GWI and died from diseases other than ALS. She also called for better coordination between VA hospitals so that VA studies being conducted in one region of the country such as Dr. Amin's study of sleep apnea could be expanded in order to allow more Gulf War veterans to participate in the research.

Ms. Louise Richard, an ill Gulf War veteran and nurse from Canada, thanked the Committee for the work it has done and spoke briefly of the lack of response she has witnessed from the Canadian government with regard to GWI research and care for its veterans.

Once all audience members were given the opportunity to speak, Chairman Binns thanked Dr. Sullivan for putting together the meeting and then thanked the speakers for their research and presentations. He adjourned the day's meeting at 5:08pm.

DAY 2

Chairman Binns opened the second day of the meeting by welcoming Dr. Joel Kupersmith, Chief Research and Development Officer (CRADO) for the Department of Veterans' Affairs. Chairman Binns also welcomed the other members from VA's Office of Research and Development including Dr. Timothy O'Leary, Director of Clinical Science, and Dr. Bill Goldberg, Gulf War Research Portfolio Manager for taking time to speak with the Committee.

Dr. Kupersmith thanked Chairman Binns for his introduction and spoke briefly of the progressive changes he has seen at the VA in recent years. He acknowledged that mistakes had been made in the past, and that he and others at the VA had learned a lot from the Committee. Dr. Kupersmith also mentioned that the new Secretary was interested in expanding exposure-related programs. Before beginning open discussion, he invited Dr. Bill Goldberg to provide an update on the VA's Gulf War research.

Gulf War Update

Dr. Bill Goldberg, Department of Veterans' Affairs

Dr. Goldberg gave a brief status update on VA funding for Gulf War research, discussed short-term funding plans and then concluded with an overview of long-term plans which gave rise to the larger discussion with Drs. Kupersmith and O'Leary and the Committee (See Appendix – Presentation 9). Research funding opportunities currently exist under three RFAs that are open to applications through mid-December. Dr. Goldberg stated that

future research of interest encompasses animal research, work on human samples, clinical studies, and treatment trials related to GWI.

Dr. Goldberg then turned the planning discussion over to Dr. O'Leary. Dr. O'Leary began the discussion by asking if the Committee saw a compelling biological rationale for any specific form of GWI treatment trial based on currently available literature.

Dr. Melling remarked that, in his opinion, the health problems from which Gulf War veterans are currently suffering most likely result from a chain of biological events that occurred over time, and that trying to develop treatments based on the original trigger (even if that exact cause were known in certainty) might not alleviate the veterans' current ailments. Dr. Melling therefore supported a symptom-based approach whereby treatment trials focus on alleviating the current symptoms that ill Gulf War veterans are experiencing. That said, he cautioned against drawing too many parallels between symptoms of Gulf War Illness and other "similar" conditions such as fibromyalgia.

Dr. White remarked that the clinical, physiological, immunological and even radiological characteristics of Gulf War veterans are so complicated and interrelated that identifying a single biological basis would be unrealistic. She would like to see a plan developed that considers the types of abnormalities and types of pathology that have been uncovered in the research so far. Dr. White stated that she believes there is a basic issue of case definition that has yet to be resolved. She remarked that the plan to attack the issue with the existing funding should be comprehensive and integrated, taking into account the coagulopathy issues, the CNS issues, the immunological issues, etc. She said she was positive that complex interrelations exist between these systems, and that the exact nature of these relationships would not be elucidated prior to the start of treatment trials. She encouraged an approach that would attempt to map out the relationships as much as possible, perhaps with input from scientists outside the VA.

Dr. O'Leary replied that he didn't see anything inconsistent in the views expressed by the Committee. Dr. Meggs commented on what he considers the promising and testable hypothesis for the causality of GWI to be. This is the hypothesis that veterans were exposed to a complex mixture of toxic chemicals at sublethal doses to an extent that some individuals' adaptive ability broke down. He cited a fitting research model developed by Hans Selye in rats, and also spoke of environmental clean room control units that could prove useful in future research.

Dr. O'Leary replied that, from a therapeutic perspective, the Committee seemed to agree that no particular avenue of clinical investigation beyond that of symptomatic relief seemed appropriate at present. Chairman Binns asked to expand a bit on that statement. He remarked that treatments exist that address certain mechanisms which are known or strongly thought to be affected in veterans with GWI, namely hypercoagulation, autonomic nervous system functioning, probably neuroinflammation, and perhaps mitochondrial damage. Chairman Binns urged Dr. O'Leary to consider this group of targets. He also emphasized the importance of veterans being advised to avoid further exposures to toxic chemicals.

LTC Knox spoke about her experience on the Presidential Advisory Committee (PAC) in the 1990s. She commented that the Committee had been responsible for looking at the existing research to attempt to find an explanation of GWI, but because no wartime exposures had been acknowledged at that time none of the research focused on that. LTC Knox recalled that her proposal that synergistic effects of chemical exposure and PB were responsible for GWI was met with great resistance at that time. She also emphasized the importance of acknowledging the physiological and not just the psychological underpinnings of GWI.

Dr. Meggs remarked that tests exist which could be used to determine whether ill veterans have heightened sensitivity to certain chemicals. He commented that pilot studies using environmental control units would be simple and relatively inexpensive.

Dr. Beatrice Golomb, a member of the Committee, supported Chairman Binns' comments, adding that she believed there to be several domains in which recognized changes correlate with pathophysiology that would represent reasonable targets for treatment trials.

Dr. O'Leary, who worked as a medical review officer for the Food and Drug Administration (FDA) in the past, expressed concern that a stronger evidence base was needed as a whole before new treatment trials would be approved. Dr. O'Leary proposed two approaches to attain this goal. First, Dr. O'Leary would like to see the creation of a large, nation-wide epidemiological cohort with cross-sectional and longitudinal features. Dr. O'Leary suggested that, if possible, the cohort should include a twin pair subset. He foresaw that the cohort size would be 10,000 or greater. He would like to characterize the individuals' illnesses more completely in order to develop the questions of symptom complex. Dr. O'Leary envisioned that various studies (e.g. neurophysiological assessments, high resolution neuroimaging, immunological assays and coagulopathy studies) would then be carried out on subsections of the cohort. Dr. O'Leary would like to see this approach combined with appropriately designed genetic studies.

Dr. O'Leary then discussed the process he envisioned. He would first ask one or more researchers to write a letter of intent outlining their planned investigation. Each letter would be subject to a scientific evaluation and, if approved, a planning committee would be created. The committee would consist of individuals recommended by the investigators as well as individuals recommended by the VA's statistical or epidemiological coordinating centers. The planning committee would meet in person three or four times. The committee would also meet by phone approximately weekly in the process of developing a study plan, which would then be submitted to a scientific evaluation committee of the Cooperative Studies Program (CSP) for independent scientific evaluation. The study plan would then be submitted for central Institutional Review Board (IRB) approval.

Chairman Binns then spoke about the process-related recommendations made by the Committee in years past (See Appendix – Presentation 10). The recommendations

included developing a comprehensive plan, utilizing a panel of experts and specialized reviewers, and managing the program as a coherent whole. Dr. O'Leary replied that these recommendations appear to be in line with the process he laid out for the future Gulf War research program.

Dr. White commented that the CSP is a powerful tool, and she saw the application of this program to GWI as a positive step. She then asked how the requests for letters of intent would be organized. Dr. O'Leary replied that the VA would be approaching people that the Committee respects. He also emphasized that the research would be conducted in cooperative fashion such that it would be a product of the agency, not just the product of individual scientific investigators. Dr. Kupersmith then commented that the CSP has been very successful in the past in various fields of investigation. He added that experts in scientific methodology could be incorporated into the process if any individuals with good research ideas who lack methodological expertise apply to the program.

Dr. Kupersmith then remarked that he hopes genetic studies can help elucidate whether some veterans were more susceptible to chemical exposures during the Gulf War. He also saw hope for the development of interventions that could possibly target the biological and chemical pathways underlying GWI symptomology. Dr. Carrolee Barlow, a member of the Committee, commented that one of the greatest values of genomic studies is their ability to lead to understanding of disease mechanisms and pathways. She remarked that such knowledge can then be used not only to identify individuals at risk, but to possibly provide therapies for those individuals already suffering from disease. Chairman Binns then asked Dr. Barlow to talk about the significance of the recommendations she had made during the Committee's review of the UT Southwestern research program. Dr. Barlow replied that ensuring an adequate population size is one of the requirements for successful genome studies attempting to identify susceptibility and risk factors. Dr. O'Leary replied that this was consistent with the VA's planned approach.

Dr. Kupersmith remarked that regardless of how an approach is implemented, someone needs to guide it. Dr. Golomb expressed her concern with a process that starts with someone centrally predetermining who should submit letters of intent (as opposed to open requests for project proposals). Dr. Golomb also asked what the budgetary considerations for the program would be. She would like to understand how the money channeled to this program might potentially infringe on funding currently going to small, pioneering studies currently underway in the field. Dr. Golomb added that although these large samples can be used to do sub-studies, it won't always be the case that the investigators with the good new ideas will be co-located with the participants in that study. Dr. O'Leary replied that the CSP is an open process and that there is nothing to preclude outside letters of intent. Dr. Golomb responded that letters of intent should be openly solicited. Dr. O'Leary acknowledged Dr. Golomb's concern, and moved on to address her other questions. He stated that the money allotted for any CSP study shouldn't compete against funding for other studies. Dr. Golomb then asked how much money would be allocated to the CSP on GWI and how much money would go toward funding other GWI research. Dr. O'Leary stated that would not be decided until the study

was designed. Dr. Kupersmith added that the VA is committed to doing what is necessary, within reason.

Dr. White then asked how long Dr. O'Leary thought it would take to launch the Gulf War CSP. Dr. O'Leary replied that it would probably reach scientific review in the spring or summer of 2010. Dr. O'Leary explained that the speed of launch after that would predominantly be determined by IRB considerations. He stated that he would be surprised if the IRB process took more than 2 or 3 months. Dr. O'Leary would like to see the launch within the current fiscal year (ending October 2010), but he could not guarantee anything.

Dr. White then stated that the use of existing cohort data should be considered in the planning of this study, particularly with regard to case definitions. Dr. O'Leary agreed.

Chairman Binns then welcomed the Chief of Staff of the VA, whom Dr. Kupersmith then introduced.

VA Briefing

Mr. John Gingrich, Chief of Staff of the Department of Veterans Affairs

Mr. John Gingrich spoke about the VA's planned course of action for the short and long-term, as it relates to Gulf War veterans. Mr. Gingrich emphasized the importance of streamlining the claims process. He stated that the first step would involve updating the internet technology (IT) system, including the creation of a virtual lifetime record for all veterans. He envisioned a VA system where the veteran is a client who has already paid with his or her service to the country. Mr. Gingrich acknowledged that VA staff members (298,000 employees) need to be attuned to the needs of veterans, and that the vast majority of them are working for the VA because they deeply care about veterans. He briefly mentioned the post-9/11 GI Bill, the American Recovery and Reinvestment Act and other examples of complex programs that the VA has been capable of managing or updating.

Mr. Gingrich then proceeded to discuss Gulf War veterans specifically. He began by noting that the Secretary of the VA has said that enough is not being done for Gulf War veterans. The VA searched for someone to head up the Gulf War Task Force, and Mr. Gingrich became its chairman. Mr. Gingrich said that the task force has set goals to identify gaps in service, look for opportunities to better serve Gulf War veterans, and seek results-oriented recommendations.

In looking at what needs to be done to move forward, Mr. Gingrich said he feels the VA must identify the key areas in need of review by consulting experts and relevant stakeholders outside of the VA. First, he stated, the VA needs to figure out what is being done within the agency. Mr. Gingrich emphasized that he wants to look holistically at the issues considering veterans' benefits, health care and future development.

Mr. Gingrich said he believes that databases need to be built and expanded. He noted that a white paper is being pulled together, and recommendations will be drawn up by January 31, 2010. He noted that the Veterans Health Administration (VHA) is also putting together an informational paper on the practices of joint proposals. Mr. Gingrich also mentioned that the VA is working on a white paper on how to increase outreach efforts to veterans. He then spoke about benefits and the Secretary's acknowledgement that improvements should be made to anticipate each veteran's benefits instead of requiring veterans to seek out and file benefits requests. Mr. Gingrich then spoke about the need for patient-centric care versus the clinician-centered care that he said currently exists across the country.

Mr. Gingrich then discussed the need for a review of clinician training and the timeline that had been decided on for this. The first client group to be served under this new clinician training system will be the Gulf War veterans. He said that the goal is to have this new system on board by May 2010.

Mr. Gingrich spoke briefly about the decision to halt funding to the UT Southwestern research program, but said that he could not discuss certain aspects in detail because the contract is still active. He said that one major mistake made in the whole process was to have implemented the agreement through a contract rather than a grant. Mr. Gingrich felt that different oversight should have been implemented, and that UT Southwestern was not solely to blame for what occurred. He stated that most of the funds already obligated would likely still be spent, but that he could not go into the issue further at a public forum due to contractual rules. Mr. Gingrich stated that his goal was to take everything that could be captured from the UT Southwestern work and apply it to the future VA GWI research program.

Dr. Golomb agreed that education programs for clinicians would help address several issues of concern that were brought up during discussion. First, she expressed her concern with the stigma that surrounded GWI for many years after the war, which she said kept some scientific researchers and members of the media from getting involved or expressing unpopular views about the etiology of GWI. She expressed her belief that education would go a long way toward rectifying that situation particularly if it were clear that the attitudes had changed. She stated that she also thinks clinician training would help improve attitudes of VA staff toward Gulf War veterans. Mr. Gingrich agreed with Dr. Golomb, stating that approaching GWI (and other issues like Agent Orange) from a holistic perspective that emphasizes the important role of exposures would help break this paradigm.

Dr. Meggs commented on the powerful tools and innovative imaging techniques that he saw developing at UT Southwestern with regard to studying GWI. He remarked that he would support any attempt to salvage the work that was begun there. Mr. Gingrich said that attempts were being made to do so, and that he shares this goal.

Dr. Bloom commended the achievements of the VA with regard to the electronic medical records system, and expressed his confidence that similar progress could be made in the other areas outlined in Mr. Gingrich's talk.

Dr. White appreciated Dr. Gingrich's interest in GWI, and commented that recent discussions held between Committee members, VA staff and others have renewed her sense of hope for the future.

Dr. Sullivan strongly supported updating the clinical training and also mentioned a need for improving the training of the VA Gulf War hotline personnel so that they can better advise these veterans.

Dr. O'Callaghan remarked that he hoped, as research moves forward, there would be an appreciation for the type of synergy that can be achieved with a large program of researchers working on both clinical and preclinical projects, as existed at UT Southwestern.

LTC Knox commended Mr. Gingrich's attitude, and expressed her desire for the products of Dr. Haley's studies to be salvaged as much as possible. Mr. Gingrich replied that contracts are subject to federal acquisition regulations, which greatly restrict the researcher's freedom. He stated that the UT Southwestern research should not have been set up under a contract for that reason.

Mr. Hardie expressed his appreciation for the effort Mr. Gingrich has put into setting up the internal task force on GWI. He agreed with Mr. Gingrich's support for a holistic approach. Mr. Hardie also suggested publicizing the existence of the Gulf War task force, namely in the Gulf War Review newsletter. He would like the 700,000 Gulf War veterans to be given the opportunity to submit input if possible. Mr. Gingrich stated that he would like to set up a website similar to the one put up for the claims process that would provide a forum for veterans to provide input. He cautioned that such a website could (and in past has) lead to an overwhelming number of responses, such that feedback and analysis could become very difficult.

Dr. Melling requested that the system by which VA research is initiated and commissioned be reviewed. Dr. Melling said he believes that getting to the endpoint required by the organization may not be achievable solely through open calls to researchers to submit proposals. Mr. Gingrich suggested that a combined approach of open proposals and targeted research should be feasible. Dr. Kupersmith replied that the results of existing VA research programs have been judged to meet veterans' needs by various reviewers, including the Inspector General. He admitted that the process could always be improved.

Chairman Binns responded to Dr. Kupersmith by stating that his assertion regrettably proved that the system is broken. He explained that VA's research over the years, as documented in the Committee's 2008 report, was largely inappropriately focused on stress. Chairman Binns then acknowledged progressive changes instigated in recent years

by several of the VA members in the room. Dr. Kupersmith replied that there was no disagreement on that matter.

Mr. Gingrich then thanked the Committee members for their service to the veterans and the country. Mr. Bunker remarked on Mr. Gingrich's caring attitude toward the soldiers during the Gulf War.

Chairman Binns thanked Mr. Gingrich for all of his efforts.

Maj. Nichols then made a plea to have the day's proceedings put up on the VA website so that other veterans could be made aware of the progress being made and the plans for future development.

Chairman Binns called for a short break, reconvening the meeting at 11:10am.

Continuation of VA Research Discussion

Dr. Kupersmith returned to the discussion by addressing the stigma of GWI. He acknowledged that this stigma applies to researchers in the field who face skepticism from other scientists, as well as to patients who have symptoms resulting from Gulf War service. Dr. Kupersmith said he thought investigators must be engaged to overcome this stigma. Dr. Golomb reiterated her support for the education process that familiarizes clinicians with the biological pathologies underlying GWI. Chairman Binns agreed, and commented that only a true sea-change on the part of VA would have an effect down through the system. Dr. Kupersmith replied that, as he understands it, the evolution of the clinical plan will spill over into research.

Dr. O'Leary then spoke about the CSP study management models. He emphasized that the system does not operate the studies directively. Rather, the management of the study reports back to the VA Director of Clinical Sciences Research and Development (currently Dr. O'Leary). Dr. O'Leary agreed that such an approach does not solve all scientific investigations, but he asserted that it has been the most successful for the VA in investigating issues like GWI.

Chairman Binns asked if there was a way to incorporate a clinical component along with the research component, so that clinicians currently seeing Gulf War veterans could provide input to the research program. Dr. Kupersmith replied that this approach would be part of the CSP, adding that over 70% of the VA researchers are clinicians. He asserted that the CSP would set up a clinical establishment that didn't currently exist, from which research efforts could feed.

LTC Knox asked if VA clinicians were advocating that Gulf War veterans donate to the tissue bank, and whether researchers were able to use tissue samples from the bank. Dr. O'Leary replied that the tissue bank focuses on the nervous system, and that Gulf War veterans do not yet suffer from a very high mortality rate, compared to other veteran populations. He stated that the tissue bank had been reasonably successful in collecting

brain tissue from veterans who had died from ALS, and that some networking with the tissue bank in Los Angeles might lead to increased accessibility. He concluded by explaining that new avenues for Gulf War research would be needed, as many of the ailments affecting Gulf War veterans appear to involve blood and mitochondria – neither of which could be studied from brain tissue samples.

Dr. Mike Weiner, from the San Francisco VA and UCSF, has used neuroimaging to study Gulf War veterans. He spoke of his surprise at learning from his study that veterans exposed to the Khamisiyah low-level sarin gas plume had significant neuropsychological impairments and significant reductions of brain gray matter. Dr. Weiner added that his research has not shown a correlation between plume exposure and any kind of symptomatology so far. He also expressed his strong support for a large, multi-site observational study using both phenotyping of symptomatology and neuropsychological assessment and biomarker research including neuroimaging techniques. He also cautioned that the impact of stress should not be forgotten, and that any future studies should document stress exposures in addition to chemical exposures. Dr. Weiner would also like to see lessons learned from Gulf War research findings applied to current troops.

Dr. Klimas remarked that her research group uses a systems-based approach to ultimately seek out a pathogenesis-based model for intervention. She mentioned that she has participated as an investigator in other CSP projects, and felt that her voice was well heard and that she was in a collaborative relationship with all other investigators, including the Principal Proponent responsible for managing the project. Speaking with regard to the Gulf War study to be pursued, Dr. Klimas agreed with the other researchers in advocating for the coordination of all the existing data so that it could be looked at in new ways and added to as research continues. She remarked that she believes subsets of GWI exist, and cautioned against leaving any ill veteran behind.

LTC Knox then urged the VA to conduct assessments on current troops, particularly those in their teens and early twenties whose brains have not fully developed. She thought comparing studies of these individuals to those of Gulf War veterans might be useful.

Dr. Sullivan asked when Dr. Weiner plans to publish his results. He replied that the spectroscopy paper was sent to JAMA but had been turned away. He has since resubmitted it, along with another paper on sarin exposure.

Mr. Hardie asked how he could go about planning in advance to have his own brain and spinal cord donated to the brain bank. Dr. O'Leary replied that states regulate organ donations to some extent, but that the brain bank CSP could provide further information. He also advised Mr. Hardie and other interested veterans to tell his VA doctor so that the request would become part of his electronic medical record. Chairman Binns asked that these instructions be disseminated to all veterans. Dr. O'Leary replied that permission would have to be obtained from VA personnel outside the Office of Research and Development.

Dr. O'Leary then moved forward with discussing the pre-clinical (animal model) leg of Gulf War research to be undertaken. In holding discussions with members of the Committee and other experts, Dr. O'Leary said he came away with a heterogeneous range of recommendations. Dr. O'Leary would like to see the development of one or more adequate animal models of disease. From his understanding, the rodent model of PB exposure aligns with the findings from human studies. Ultimately, Dr. O'Leary did not find any particular avenues of investigation to be more persuasive than any other. He also expressed his understanding of the strengths and weaknesses of rodent and primate models of disease before asking the Committee for their input.

Dr. Golomb suggested first looking for objective markers in animal models that are observed in ill Gulf War veterans such as similar autonomic nervous system indicators, including heart rate variability and coagulopathy. She cautioned that reduced activity levels in animal models could not be used as a correlate to fatigue in humans with GWI.

Dr. Bloom commented that non-human primates provided a valuable model for aging and Alzheimer's disease research, but that he would be hesitant to use non-human primates in Gulf War research at least until current studies (e.g. those started at UT Southwestern) have been completed. Chairman Binns supported Dr. Bloom's comments. Dr. White agreed that insufficient data exists in other animals to move forward with designing a study involving primates. Dr. Golomb also agreed, clarifying that her earlier remarks were not advocating the use of primates. Dr. O'Leary drew the conclusion that a hybridized, layered approach that focuses on varied investigator-initiated research was needed.

Dr. Bloom suggested that Dr. O'Leary organize a one-day conference convening individuals from the VA's animal research centers with experts who have developed animal models for other disease entities such as substance abuse models. Dr. O'Leary expressed interest in this idea, and added that he has also been interested in looking at genetic strain variation effects in rodents, which he hoped could lend clues to understanding GWI. Dr. Golomb agreed, remarking that talented investigators previously not involved in Gulf War research might come forward if given the opportunity to learn about GWI and the potential role their research could play in it.

Dr. Goldberg then called attention to the unusually large monetary incentives attached to the recently released RFAs. He expressed hope that this would provide additional incentives for researchers to pursue Gulf War research.

Dr. White expressed her concern about losing track of exposure assessment in the epidemiology study. She noted that this could be an important bridge between the epidemiology and pre-clinical studies. Dr. White stated that there are sources of information and ways to assess exposures (beyond the plume models) that could be put to better use in a systematic way. Dr. O'Leary replied that concerns exist with self-reported exposure. Dr. White stated that she believes there is classified and recently unclassified information that could shed further light on certain Gulf War exposures. Dr. O'Leary said

he would be working as closely as possible with the defense health programs to get any and all information.

Dr. Sullivan expressed her optimism regarding biomarker research, noting that the previous day's proceedings provided considerable insight into the promise of that area of Gulf War research.

Maj. Nichols encouraged all researchers applying for Gulf War funding from the VA to read the Committee's reports and recommended list of published studies. She cautioned that without this background reading the research would not be appropriately targeted. Maj. Nichols also expressed concern that the brain banking is not currently sufficiently accessible to Gulf War veterans that have been dying. Dr. O'Leary replied that he would try to better disseminate information, but that he did not have the authority to make any specific commitments.

Dr. Dorsher saw a need for broader perspectives that attempt to link in the various systems affected in ill Gulf War veterans in order to develop effective treatments more rapidly. Dr. O'Leary replied that gathering a large, multi-site epidemiological cohort would allow for the aggregation of symptom complexes into target populations which could then lead to treatment trials.

Chairman Binns then thanked everyone for participating, and stated that the day's discussion was only a beginning. He remarked that it would be necessary to develop a comprehensive plan that draws on extensive input prior to implementing the research program. Chairman Binns concluded the discussion by reiterating that the Committee does not believe that stress is on a par with toxic exposures in explaining GWI. He also urged the VA to make the best possible use of the data produced by the research begun at UT Southwestern.

Committee Business & Planning for 2010

Chairman Binns, Committee Chairman
Dr. Sullivan, Committee Scientific Coordinator

Chairman Binns first outlined the annual operations plan, including detailed 2010 objectives and priority areas of research (See Appendix – Presentation 11).

Dr. Melling liked the idea of meeting with VA researchers, but he expressed concern that Mr. Gingrich might have to use his influence to ensure that those researchers who should meet with the Committee members would. Chairman Binns said that the VA had been cooperative in the past, so he was optimistic that such meetings would be feasible. LTC Knox expressed concern that more attention be paid to treatments.

Maj. Nichols asked if any survey could be put up on the Committee's website so that VA physicians could provide feedback to help direct research and collect information. Dr. Goldberg replied that such an approach might work down the road, once an integrated care model was set up. Dr. Golomb commented that almost all of her ill Gulf War veteran

patients have tested positive for sleep apnea. She added that many have benefitted from CPAP treatment. She thought the type of survey Maj. Nichols suggested would pick up on this type of symptomology. Dr. Golomb also expressed interest in collecting patient input regarding treatments they have found useful. Chairman Binns didn't think putting a survey on the Committee's website would make a large enough impact, but suggested spreading it through VA avenues.

Mr. Bunker cautioned against concluding that large populations of Gulf War veterans suffer from fibromyalgia and chronic fatigue syndrome. He added that all clinicians treating Gulf War veterans with standard medications for chronic fatigue syndrome or fibromyalgia should be directed to take non-responsive patients off these medications. Mr. Bunker also recommended that any Gulf War veteran with abnormal sleep study results that do not fit neatly into the category of sleep apnea should be recommended to undergo further testing in line with Dr. Amin's studies.

Dr. Sullivan remarked that even symptom-based treatment can functionally help patients. LTC Knox commented that the first line sleep aid medications don't affect sleep architecture, and that the VA needs to understand what the sleep experts are doing for treatment of disordered sleep. Mr. Bunker and Dr. Golomb expressed support for the mitochondrial and oxygenation theory underlying GWI. Maj. Nichols agreed that oxygen greatly helped alleviate her symptoms as well.

Committee Recommendations on Recent VA's RFAs

Dr. Sullivan then presented the Committee's concerns and recommendations made regarding the new VA Gulf War RFAs (See Appendix – Presentation 12).

Dr. Goldberg replied during Dr. Sullivan's presentation to respond to her question as to whether the VA would provide Gulf War registry participants' contact information to funded investigators so that they could recruit for the new clinical studies. He replied that the registry contact information could not be given out without IRB approval. Dr. Goldberg acknowledged that participant recruitment is a real problem for all investigators. Mr. Bunker replied that the names from the Gulf War registry go into a database which is used to send out the Gulf War Review. He suggested that any study recruiting Gulf War veterans should advertise in the Gulf War Review. Dr. Goldberg remarked that some centralized mechanisms for research recruitment do exist, noting that all clinical trials must be registered at clinicaltrials.gov, which is responsible for publishing nationally advertised recruitment notices.

Dr. Sullivan then continued with her presentation, remarking on the veterans' concerns that the brain bank data be shared with investigators. Dr. Goldberg responded that no data on the tissue exists, and that the brain bank serves only as a collection and storage unit.

After Dr. Sullivan completed her review of the recommendations, Mr. Hardie read from a document of his RFA-related recommendations focused broadly on priorities he has regarding overall research goals, the focus on treatment and additional foci. Mr. Hardie

felt strongly that studies whose principal focus is on psychiatric disease or psychological stress as the primary cause of GWI should not be funded. He emphasized the importance of finding treatments for ill Gulf War veterans, specifically those targeting functional status, symptom complexes, measurable clinical outcomes, and GWI subgroups. Mr. Hardie would like to see proposals that involve research of objective indicators of biological processes or abnormalities in GWI. These areas include central nervous system structure and function, central neuroinflammatory processes, neuroendocrine measures, autonomic nervous system function, immune parameters, indicators of chronic infection, overlaps between systems, and genetic, genomic, proteomic, or metabolic characteristics.

LTC Knox suggested advertising for study recruitment on DoD paystubs. Dr. Goldberg reiterated that legal restrictions exist which constrain the way research can be advertised.

Chairman Binns then called for the public comments section to commence, starting with members of the audience who had not yet spoken during the day.

Public Comments

Ms. Louise Richard briefly spoke about the nutritional deficiencies that could result from the severe gastrointestinal issues suffered by many ill Gulf War veterans. She described the intravenous vitamin injections she regularly receives from her environmental doctor in Canada, a treatment that she said provides her with improved energy for several days following the injection. Chairman Binns thanked Ms. Richard, and expressed his appreciation for the knowledge that veterans offer to clinicians treating GWI.

Mr. Donald Overton, Executive Director for Veterans of Modern Warfare, thanked the Committee for its work and the release of the 2008 report. He remarked that, as a result of the report's release, veterans were becoming active in the veteran service community. Mr. Overton also commented on the momentum he had recently seen on Capitol Hill as well. Dr. Goldberg then reflected on the briefing that Mr. Gingrich had given on the Hill, remarking that he held nothing back and that the goals set would be followed by action.

Maj. Nichols encouraged the dissemination of case studies in peer review journals. She also thanked the Committee for its transparency. Maj. Nichols then requested that a phone line be set up so that veterans would be able to call in and listen to the Committee meeting proceedings. She also expressed enthusiasm for getting Gulf War veterans tested for the XMRV retrovirus linked to some cases of chronic fatigue syndrome. Dr. Klimas said that veterans' existing samples had already been pulled and sent to be tested.

Mr. Bunker then commented on the problems he and other veterans had experienced getting in touch with people at the VA who were aware of the War-Related Injury and Illness Centers (WRIISCs). He also expressed concern over the need for a standardized definition of GWI and said he strongly supports the use Dr. Lea Steele's GWI definition.

Chairman Binns then thanked the Committee and adjourned the meeting at 1:36pm.