

Research Advisory Committee on Gulf War Veterans' Illnesses

February 23-24, 2009, Committee Meeting Minutes

University of Texas Southwestern
Dallas, TX

DEPARTMENT of VETERANS AFFAIRS



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



I hereby certify the following minutes as being an accurate record of what transpired at the February 23-24, 2009 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
Floyd Bloom
Beatrice Golomb
Joel Graves
Marguerite Knox
Bill Meggs
James O'Callaghan
Lea Steele
Adam Such
(Carrolee Barlow) – participated by phone

Committee Staff

Kimberly Sullivan
Sadie Richards

Designated Federal Officer

William Goldberg

Guest Speakers

Ron Killiany
Chris Filley

Additional Speakers – University of Texas & Sub-Contractors

Carla Bann
Richard Briggs
Sergey Cheskov
Munro Cullum
Thomas Ferree
Kaundinya Gopinath
Robert Haley
John Hart
Vince Iannacchione
Mike Kraut
Hanzhang Lu
Roderick McColl
Timothy Odegard
Mette Posamentier
Wendy Ringe
Bart Rypma
Jeffrey Spence
Dixie Woolston

ABBREVIATIONS

ALS – Amyotrophic Lateral Sclerosis

ASL – Arterial Spin Labeling

BIRN – Biomedical Informatics Research Network

CATI – Computer Assisted Telephone Questionnaire

CBF – Cerebral Blood Flow

CDC – Center for Disease Control

CFI – Comparative Fit Index

Cho – Choline

Cr – Creatine

DoD – Department of Defense

DTI – Diffusion Tensor Imaging

DSDL – Dorsal Striatum – Dorsolateral PFC

DSVT – Digit-Symbol Verification Task

EEG – Electroencephalography

FAB – Frontal Assessment Battery

fMRI – functional Magnetic Resonance Imaging

GWV – Gulf War Illness

IRB – Institutional Review Board

MRG – Merit Review Group

MRI – Magnetic Resonance Imaging

MRS – Magnetic Resonance Spectroscopy

MS – Multiple Sclerosis

MTL – Medial Temporal Lobes

NAA – N-Acetyl Aspartate

OP – Organophosphorus/Organophosphate

OPIDN – Organophosphate Induced Delayed Neuropathy

PB – Pyridostigmine Bromide

PESD – Post-Exposure Stress Disorder

PET – Positron Emission Tomography

RMSEA – Root Mean Square Error of Approximation

SPECT – Single Photon Emission Computed Tomography

SRMR – Standardized Root Mean Square Residual

T – Tesla

TLI – Tucker-Lewis Index

USMHS – United States Military Health Survey

UTSW – University of Texas Southwestern

VA – Veterans' Affairs

VFW – Veterans of Foreign Wars

VISN – Veterans Integrated Service Network

VSVM – Ventral Striatum Ventromedial PFC

WM – Working Memory

WMSA – White Matter Signal Abnormality

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

February 23-24, 2009

University of Texas Southwestern, T. Boone Biomedical Bldg., Third floor, Room NG3.202,
6001 Forest Park Road, Dallas, TX

Agenda

Monday, February 23, 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 – 9:15	White matter and behavioral neurology	Dr. Christopher Filley University of Colorado Denver VAMC
9:15 – 10:00	MRI techniques in GW studies	Dr. Ron Killiany Boston University
10:00 -10:30	White matter disease and neuroimaging discussion	Dr. Christopher Filley Dr. Ron Killiany
10:30 – 10:45	Break	
10:45 – 11:15	Preliminary results of UTSW Gulf War program: Overview	Dr. Robert Haley University of Texas Southwestern VA Dallas Healthcare System and UTSW staff
11:15 - 12:30	Preliminary results of UTSW Gulf War program: Neuroimaging	Dr. Robert Haley and UTSW staff
12:30 – 1:30	Lunch	
1:30 – 3:00	UTSW Gulf War program Neuroimaging discussion	Dr. Robert Haley and UTSW staff
3:00 – 3:15	Break	
3:15 – 4:15	UTSW response to RAC recommendations & discussion with Committee: Animal Studies	Dr. Robert Haley and UTSW staff
4:15 – 4:45	UTSW response to RAC recommendations & discussion with Committee: Other Clinical Studies	Dr. Robert Haley and UTSW staff
4:45 - 5:15	Public comment	

**Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses
February 23-24, 2009**

**University of Texas Southwestern, T. Boone Biomedical Bldg., Third floor, Room NG3.202,
6001 Forest Park Road, Dallas, TX**

Agenda
Tuesday, February 24, 2009

- | | | |
|----------------------|--|---|
| 7:45 – 8:15 | Informal gathering, coffee | |
| 8:15 –9:15 | UTSW response to RAC recommendations
& discussion with Committee:
Survey Results | Dr. Robert Haley
University of Texas Southwestern
VA Dallas Healthcare System
and UTSW staff |
| 9:15 – 10:15 | UTSW response to RAC recommendations
& discussion with Committee:
Case Definition | Dr. Robert Haley
and UTSW staff |
| 10:15 – 10:30 | Break | |
| 10:30 – 11:15 | UTSW response to RAC recommendations
& discussion with Committee:
Sample Size | Dr. Robert Haley
and UTSW staff |
| 11:15 – 12:00 | UTSW response to RAC recommendations
& discussion with Committee:
DNA Study | Dr. Robert Haley
and UTSW staff |
| 12:00 – 1:00 | UTSW response to RAC recommendations
& discussion with Committee:
General recommendations | Dr. Robert Haley
and UTSW staff |
| 1:00 – 1:30 | Public comment | |
| 1:30 | Adjourn | |

Day 1

The February 23-24, 2009 meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses (hereinafter referred to as the Committee) was held in Room NG3.202 of the T. Boone Pickens Biomedical Building at the University of Texas Southwestern, 6001 Forest Park Road, Dallas, TX.

Welcome, introductions & opening remarks

Mr. James Binns, Committee Chairman

Chairman Binns called the meeting to order at 8:30am.

White matter and behavioral neurology

Dr. Christopher Filley

University of Colorado & Denver VAMC

Dr. Filley began with an orientation to the field of behavioral neurology, then outlined clinical historical studies and described the significance, physiology and diseases of white matter (Appendix – Presentation 1). Dr. Filley also described the different non-invasive techniques currently being used to study white matter in living subjects. These methods include magnetic resonance imaging (MRI), magnetic resonance spectroscopy (MRS), diffusion tensor imaging (DTI), positron emission tomography (PET), and functional magnetic resonance imaging (fMRI). Dr. Filley then summarized the findings of several studies he has conducted on white matter dementia, toxic leukoencephalopathy, and toluene encephalopathy. Drawing on the findings of his own research and other research cited in the report released by the Committee in November 2008 (hereinafter referred to as the RAC Report), Dr. Filley remarked on the probable role of white matter degeneration in Gulf War Illness.

After Dr. Filley's presentation, Rev. Joel Graves asked how the myelin sheath can become inflamed. Dr. Filley responded that neuroinflammation could be triggered by a variety of different biological mechanisms, often giving rise to white matter degradation.

Dr. Bill Meggs then commented that in his practice he has seen patients who have psychiatric disability but normal MRI scans. He asked Dr. Filley how sensitive MRI scans are to this type of neural damage. Dr. Filley responded that his study used a .35 Tesla (T) magnet, and that it would sometimes take 4-6 years before symptomatic patients would have abnormal MRI scans. He added that current technology and improving techniques should allow doctors to identify patients earlier.

At 9:20am Chairman Binns introduced Dr. Ron Killiany.

MRI Techniques in Studies of Gulf War Veterans

Dr. Ron Killiany

Boston University School of Medicine, BU School of Public Health, Brigham & Women's Hospital, Harvard Medical School & Massachusetts General Hospital

Dr. Killiany focused his presentation on his use of MRI techniques to study white matter diseases (Appendix – Presentation 2). Commenting on the significance of these studies with respect to Gulf War Illness (GWI), Dr. Killiany remarked that typical GWI symptoms include features found in white matter diseases. In discussing the variety of tools that exist to analyze (or “post-process”) brain scan images, Dr. Killiany praised the federally-funded Biomedical Informatics Research Network (BIRN) – a group of scientists whose mission it is to develop tools for use by other scientists in processing imaging scans. Dr. Killiany noted that imaging is a particularly useful technique because it provides a resource of scanned images that can be studied and shared indefinitely, without being used up. Dr. Killiany acknowledged that post-processing techniques can run up against issues of standardization and reliability. Challenges of studying white matter, such as determining the boundary between gray matter and white matter in aging individuals, were also discussed in this presentation. After reviewing recent research, Dr. Killiany made suggestions for future imaging research, calling for a national initiative and standardization of approaches. He also remarked that, in order to be validated, a model for GWI must be tested on a set of subjects different than those individuals from whom the model was generated.

Chairman Binns then opened the floor to questions for Drs. Filley and Killiany.

White Matter Disease and Neuroimaging Discussion

Dr. Christopher Filley

Dr. Ron Killiany

Dr. Peter Pressman, a clinician from the United States Navy, then asked if Drs. Filley and Killiany could speculate about the neurophysical signs of inflammatory damage. He also asked Dr. Filley to comment on his experience with treatment management, and whether he saw potential applications for blockers of inflammatory cytokines and/or high dose statins or steroids.

Dr. Filley replied that using MRS to look at pathophysiology has allowed clinicians to identify neuronal and myelin sites of injury without invasive procedures. He explained that decreased levels of NAA (N-Acetyl Aspartate), which can be detected by MRS, indicate that axons have been damaged. Normal NAA levels signify that the axons are still intact, and that treatments encouraging myelin regeneration might be effective. These potential “remyelination” treatments (e.g. genetic therapy, stem cells) are still being researched. High choline (Cho) levels indicate active inflammation with demyelination. High levels of choline can be treated with steroids or other anti-inflammatory treatments. However, in several Gulf War studies Dr. Filley reviewed, choline levels were not high. Dr. Filley emphasized that the treatment protocol would depend on the pathology of the particular disease.

Dr. Killiany added that white matter signal abnormalities (WMSAs) do not appear to be increasing in Gulf War veterans, which suggests that demyelination is not occurring. He

acknowledged that MRS has gone through a dark history but is likely to re-emerge as a powerful research tool, particularly through the utilization of whole brain (“voxel by voxel”) MRS, which he believes will help identify more subtle neural changes earlier.

Dr. Bill Meggs, a member of the Committee, asked how good SPECT scans are in assessing toxic neuroencephalopathy. Dr. Filley replied that the advantage of SPECT is its relative low cost, but in his opinion it has little use in this (or other) research. He added that PET scanning is useful, as is fMRI for more elegant depictions of cortical functions.

Dr. Floyd Bloom, a member of the Committee, asked how one goes about discriminating between psychiatric syndromes with white matter abnormalities vs. disorders of the white matter. Dr. Filley replied that white matter disorders are those *known* disorders of the white matter diagnosed by a neurologist. There are also known psychiatric diagnoses (e.g. schizophrenia) or syndromes for which the clinical symptoms are the only criteria used to determine diagnosis.

Dr. Bloom pointed out the difficulty of drawing conclusions from studies of veterans for whom there is no data on pre-deployment history or MR evidence. Dr. Filley acknowledged the significant reality of this concern.

Randy Stamm, an ill Gulf War veteran, asked how many GW veterans had been diagnosed with Amyotrophic Lateral Sclerosis (ALS), following up with an anecdotal story of one of his soldiers currently suffering from ALS. He also asked whether there would be another round of GW testing in the future. Dr. Filley did not have a number, but replied that GW veterans were diagnosed at a higher frequency and at a younger age than their non-deployed counterparts and the general public.

Dr. Jim O’Callaghan asked Dr. Filley if proteomic profiling has progressed for multiple sclerosis (MS). Dr. Filley was not aware of any progress, though routine MRI has proven useful in monitoring progression of the disease.

LTC Marguerite Knox, a member of the Committee, commented on the wide range of symptoms and inconsistent neuropathologies associated with MS, and asked whether any NAA research was being done in these patients. Dr. Filley acknowledged the importance of this “normal appearing” white matter phenomenon, and pointed out that what looks normal in an MRI may not actually be normal – and this is where MRS and DTI can be useful for providing more finely tuned analyses to enable more accurate correlations with clinical status.

Dr. Kim Sullivan, scientific coordinator for the Committee, remarked on the importance of studying structural *and* functional relationships. Dr. Filley agreed. Dr. Killiany remarked that, in some ways, these WMSAs are actually detrimental to the study of white matter because they may not be the central feature of the disease being studied.

Dr. Pressman asked Drs. Filley and Killiany if they have thought of a standardized approach or package of neuropsychological screening instruments that could be used in the field to evaluate Gulf War veterans who present with leukoencephalopathic symptoms. Dr. Filley recommended the frontal assessment battery (FAB), or a similar test which is sensitive to dysexecutive

syndromes, sustained attention problems, and other symptoms commonly documented in veterans with GWI.

Mr. Mike Hood, a Gulf War veteran and service officer for the VFW, brought up his concern over the non-standardized medical protocol for Gulf War veterans, and the lack of diagnostic coordination between the various health care systems that veterans seek care through. Dr. Filley acknowledged the importance of Mr. Hood's concerns.

David Boone, a rheumatologist in the audience, asked if and how chronic pain can be explained on a white matter disease basis. Dr. Filley replied that primary white matter pathology without vascular involvement is painless most of the time. Dr. Killiany added that, although he and Dr. Filley are focused on white matter features potentially central to GWI, he doubts that white matter components alone will account for everything related to the disorder.

Another member of the audience asked Drs. Filley and Killiany if they could comment on the tasks they used to diagnose memory retrieval difficulties. Dr. Filley said that the most basic test he typically uses is the three-word recall test.

In response to the question about chronic pain, Dr. Meggs remarked that GWI, like most toxic illnesses, is a multi-system disease that must be diagnosed and studied as such. Dr. Meggs then asked Dr. Killiany how likely it was that the results of his data-driven morphometry study were due to chance. Dr. Killiany replied that data-driven analyses (including his exploratory research) could not be used to draw any conclusions, though they might be useful in postulating disease models.

Dr. Timothy Odegard, of UT Southwestern, asked Dr. Killiany about his interpretation of the NAA, which he added was also present in the cell body. Dr. Filley interjected that he only looked at white matter (myelin vs. axonal degeneration). Dr. Odegard followed up with a query about the technique used (e.g. single voxel spectroscopy, placement of the voxel). Dr. Filley responded that his study of lupus looked at the white matter frontal area. Dr. Killiany added that although NAA is found in cell bodies, it is found in higher concentrations in the white matter.

Dr. Sullivan asked if there are any medications or supplements that might be helpful for remyelination. Dr. Filley replied that nothing is close to market-ready, or ready for clinical use. He commented that spontaneous remyelination does occur, and basic neuroscientists are currently studying this.

Dr. Beatrice Golomb asked about the potential impact of excessive antibodies to squalene (thought to be present in a subgroup of Gulf War veterans) on demyelination. Dr. Filley had not heard of squalene antibodies.

At 10:35am Chairman Binns concluded the discussion session and called for a break.

At 10:53am Chairman Binns reconvened the meeting and thanked Dr. Robert Haley for hosting.

Preliminary results of UTSW Gulf War program: Overview

Dr. Robert Haley, University of Texas Southwestern

Dr. Haley presented an overview of the status of several components of the UTSW Gulf War program, including an update on the national survey and tissue bank, and the neuroimaging studies (Appendix – Presentation 3). Dr. Haley stated that the biomarker studies were not presented because the data could not be analyzed due to a contracting problem.

Before his research team began their presentations, Dr. Haley was asked by Chairman Binns to describe the syndrome groups being studied. Dr. Haley then gave an overview of the syndromes into which he categorized the study participants, explaining that the syndromes were developed by factor analysis of symptoms exhibited in the group of Gulf War Navy Seabees originally studied at UTSW in 1997. Dr. Haley defined Syndrome 1 as mild impaired cognition. Syndrome 2 subjects exhibit “confusion ataxia” including mild dementia, episodes of confusion and vertigo. Veterans classified within Syndrome 3 experience severe pain problems. Some symptoms, including diarrhea and muscle weakness, are experienced by all syndrome groups. Dr. Haley noted that the studies conducted thus far compared two groups of subjects – one group being the control group of well, non-deployed Gulf War veterans, and the other consisting of Gulf War Navy Seabee veterans identified by Dr. Haley as exhibiting characteristics of “Syndrome 2.” Dr. Haley noted that since the studies are ongoing, researchers remain blind to each participant’s identified syndrome, and thus refer in their presentations to Group A and Group B.

Gulf War Illness and Chemical Agent Exposure Program – Human Studies Component Organization

Dr. Richard Briggs, University of Texas Southwestern

Dr. Briggs began by thanking the veterans who have participated in the UTSW studies. He then briefly presented the basic organization of the UTSW studies (Appendix – Presentation 4) prior to introducing Dr. Sergey Cheshkov.

Magnetic Resonance Spectroscopy Findings

Dr. Sergey Cheshkov, University of Texas Southwestern

Dr. Cheshkov presented on the research group’s preliminary MRS study findings, which identified lower ratios of NAA:Creatine(Cr) in certain brain regions of participants in Group A compared to Group B (Appendix – Presentation 5). These between group differences were found in the left hippocampus and both in the right and left basal ganglia.

Task Order 4.2

Dr. Hanzhang Lu, University of Texas Southwestern

Dr. Lu presented on the status of his MRI research investigating the change in cerebral blood flow (CBF) following cholinergic stimulation in Navy Seabees versus controls (Appendix –

Presentation 6). The preliminary results of this research found increased CBF in Group A following physostigmine exposure, whereas CBF decreased in Group B (as would be expected in “normal” individuals following cholinergic activation).

Statistical Re-Analysis of the Cholinergic Challenge Experiment

Dr. Jeffrey Spence, University of Texas Southwestern

Dr. Spence, a statistician for Task Order 4.8, presented data on the re-analysis of the cholinergic challenge experiment described above (Appendix – Presentation 7). This study confirmed that MRI-based Arterial Spin Labeling (ASL) can be used in place of SPECT to measure CBF. The preliminary results confirmed that CBF was decreased in Group B and was elevated in Group A following cholinergic (physostigmine) stimulation.

Diffusion Tensor Imaging

Dr. Roderick McColl, University of Texas Southwestern

Dr. McColl discussed the results of the DTI component of the study (Appendix – Presentation 8). This preliminary study found increased mean and perpendicular diffusion (of water into the axons/white matter) in Group A compared to Group B. Dr. McColl reported that these findings suggest that Group A may suffer from white matter damage, since the myelin sheath that coats healthy neurons normally repels water.

Preliminary VBM Analyses in GW Veterans

Dr. Dixie Woolston, University of Texas Southwestern

Dr. Woolston presented preliminary findings of the Voxel-Based Morphometry (VBM) analyses (Appendix – Presentation 9). Initial results suggest that Group A has significantly less white matter volume than Group B.

EEG Sub-core (Task Order 4.6)

Dr. Thomas Ferree, University of Texas Southwestern

Dr. Ferree provided an overview of the EEG study component (Appendix – Presentation 10). This study found that Group A exhibited global “EEG slowing” and reduced alpha activity to visual stimuli compared to Group B, which the researchers believe indicates reduced input from the ascending activating system.

Neurocognitive Findings in Gulf War Illness

Dr. Munro Cullum, University of Texas Southwestern

Dr. Cullum, a clinical neuropsychologist, presented preliminary findings from Task Order 4.7 (Appendix – Presentation 11). This MRI study found mild neuropsychological impairments in the domains of executive function, declarative memory, working memory & sustained attention/concentration in Group A compared to Group B. When compared to results of a 1998 SPECT study of the same cohort, 7 out of 10 Group A participants exhibited slight functional decline.

Task Order 4.11 - Memory Encoding and Recognition

Dr. Wendy Ringe, University of Texas Southwestern

Dr. Ringe presented her behavioral and structural (fMRI) research findings on functional memory encoding and recognition in the medial temporal lobes (MTL) (Appendix – Presentation 12). Preliminary findings from the study showed impaired memory recognition and decreased MTL activation in Group A compared to Group B.

Task Order 4.14 – Auditory-Visual Conjunctive Memory

Dr. Timothy Odegard, University of Texas Arlington

Dr. Odegard presented his research comparing memory and hippocampal activity in healthy young adults and participants in Groups A and B (Appendix – Presentation 13). His preliminary fMRI study found that Group A exhibited deactivation in several regions of the left hippocampus involved in memory encoding compared to Group B and young healthy adults.

Task Order 4.12 – Attention (CPT), Inhibition (SST)

Dr. Mette Posamentier, University of Texas Southwestern

Dr. Posamentier presented an overview of her study which used several measures, including EEG and fMRI, to investigate sustained attention and response inhibition in Groups A and B (Appendix – Presentation 14). She reported that the results are still being analyzed.

Prefrontal Function in GW Veterans - Task Order 4.12

Dr. Bart Rypma, University of Texas Southwestern

Dr. Rypma reviewed findings from his fMRI study of working memory (Appendix – Presentation 15). His results suggested that, in Group A, the frontoparietal circuit that normally allows for efficient and effective white matter processes (e.g. executive functions) is compromised, leading to engagement of compensatory processes.

At the conclusion of Dr. Rypma's presentation, Chairman Binns thanked the morning's presenters and dismissed the Committee for lunch.

Chairman Binns reconvened the meeting at 1:48pm.

Word Finding/Semantic Memory Project

Dr. John Hart, University of Texas Dallas

Dr. Hart, a VA doctor, presented the results from a study that he conducted to evaluate object retrieval in Gulf War veterans (Appendix – Presentation 16). Dr. Hart found that Group A had more difficulties with semantic memory recall tasks, and that particular areas of the brain (thalamus and other dopaminergic areas) were not activated in Group A during the recall tasks.

At the conclusion of his presentation, Rev. Joel Graves, a member of the Committee, asked Dr. Hart what dopamine agonist he mentioned giving to several patients (not in the current study) who exhibited word finding/semantic memory problems. Dr. Hart replied that the medication was bromocryptine but that he would not widely recommend the medication.

fMRI of Complex Verbal Functions in GWS

Dr. Richards Briggs, University of Texas Southwestern

Dr. Briggs presented his fMRI research on the reduced activity of the basal ganglia and several other brain regions in Group A during word generation tasks (Appendix – Presentation 17).

Emotional Memory Circuit Project

Dr. Mike Kraut, Johns Hopkins University

Dr. Kraut presented his research findings on Group A's hyperarousal to emotional stimuli, which he referred to as Post-Exposure Stress Disorder (PESD). (Appendix – Presentation 18).

Fronto-Striatal Systems in Depression & Gulf War Illness

Dr. Wendy Ringe, University of Texas Southwestern

Dr. Ringe presented preliminary fMRI results from her study of basal ganglia activation in response to emotional stimuli (Appendix – Presentation 19). Dr. Ringe's study found that the two participant groups differed in their reactions to emotional pictures, but the role of depression, which was commonly found in the Syndrome 2 group, is not well understood.

Quantitative Sensory Testing (OST) fMRI of GW Veterans

Dr. Kaundinya Gopinath, University of Texas Southwestern

Dr. Gopinath assessed differences in neural pain activation in Group A compared to Group B (Appendix – Presentation 20). Preliminary results suggest that participants in Group A have higher activation in certain brain areas (hyper-reactivity to pain stimuli).

Basal Ganglia Functional Connectivity in GWI

Dr. Kaundinya Gopinath, University of Texas Southwestern

Dr. Gopinath then presented another fMRI study which preliminarily found that certain neural connections in the basal ganglia related to attention and self-monitoring were more active in Group A than Group B (Appendix – Presentation 21).

Take-Home Points

Dr. Robert Haley, University of Texas Southwestern

Dr. Haley then summarized the overall study findings, namely that most studies showed substantial differences between Group A and Group B and that the evidence doesn't favor one mechanism over another for these differences (Appendix – Presentation 22).

Chairman Binns then thanked Dr. Haley and the UTSW research team. He also acknowledged that no discussion of the UTSW clinical trials would take place, due to contractual issues mentioned by Dr. Haley. Chairman Binns then opened the floor to discussion of the neuroimaging studies.

Neuroimaging Discussion

Chairman Binns began the discussion by asking how UTSW researchers will select a maximally efficient battery of tests among the many being explored to affect the relevant diagnoses. He first asked which studies are the most promising diagnostically (i.e. in their ability to distinguish between ill and well veterans). Chairman Binns then asked Dr. Haley what studies of which groups (Seabees, monozygotic twins, etc.) are the most relevant.

Dr. Haley responded that the current plan is to analyze the Seabees data, weed out unpromising studies, and improve efficiency by replacing SPECT with ASL and by reducing neuropsychological testing. Dr. Haley acknowledged that his team would either have to conduct more tests on fewer subjects or run fewer tests on more subjects. He restated that the original objective of the survey study was to determine whether the results found in the Seabees could be generalized to the GW population in general. Dr. Haley recognized that new goals might need to be set.

Chairman Binns then asked Dr. Haley about the status of the remaining Seabee “Syndromes” being studied at UTSW. Dr. Haley responded that, in analysis of the survey to be discussed on Tuesday, Syndrome 4 appears to be very different from, but as severe as, Syndrome 2. Syndromes 5 & 6 can probably be discounted.

Dr. Beatrice Golomb, a member of the Committee, asked Dr. Haley what fraction of ill GW veterans meets Syndrome 2 criteria. Dr. Haley stated that he did not know. Dr. Steele replied that she thought the number was about 10%. Dr. Golomb then stated that Dr. Haley’s results did not surprise her very much, since Syndrome 2 subjects exhibit pronounced CNS phenotypes. She then emphasized the importance of research looking outside the brain. Dr. Golomb then remarked that the question still remains as to whether the difference in presentation is due to different mechanisms on a similar substrate, or the same mechanism acting on different substrates, or some combination of these two possibilities. Lastly, Dr. Golomb commented that increased and decreased activation of different brain regions doesn’t necessarily represent compensation, and could be a sign of contribution.

Dr. Lea Steele, a member of the Committee, raised a concern about Dr. Haley’s focus on Syndrome 2, which is not representative of typical ill GW veterans (in that they present severe CNS symptoms, including many with major depression). She expressed reservations about choosing which neuropsychological and neuroimaging studies should be used to diagnose GWI based on studies of this atypical group of subjects (including Syndromes 1 and 3). Dr. Haley replied that Tuesday’s discussion would address this concern. He added that the debate over depression was continuing, but that most Seabees exhibiting depression did not have major depression, but rather were exhibiting depression not otherwise specified (NOS). Melanie Biggs, a clinical psychologist at UTSW, confirmed that these cases of depression were not major depressive disorder because the cause of depression could not be discerned. Dr. Steele replied that the larger (less discriminating) literature on GWI does not identify depression of any type in more than 1/3 of ill GW veterans. Dr. Haley noted that depression appeared to be one of the many symptoms linked together in a particular subset of GW veterans (Syndrome 2), but that it is difficult to identify which symptoms in ill GW veterans are linked to the war and which are not. Col. Knox pointed out that the depression diagnoses aren’t standardized between the different UTSW studies.

Dr. Kim Sullivan, the Committee’s Scientific Coordinator, remarked that she would like to see the group size exponentially larger, including more veterans without depression. Dr. Haley replied that he believed the survey study would find that ~80% of the Syndrome 2 subjects have depression. Dr. Sullivan replied that existing studies suggest that no more than 20% of treatment-seeking ill GW veterans suffer from depression. Dr. Haley responded that this reduced percentage finding was due to the broad definition of GWI put forth by the Center for Disease Control (CDC), compared to his “factor analysis.” He stated his belief that the CDC case definition includes many people who do not actually suffer from Gulf War illness. Dr. Sullivan remarked that the Committee’s concern centers on whether the factor analysis of Syndrome 2 actually self-selects for depression. Dr. Haley expressed doubt that depression would exhibit the brain imaging differences that his studies have shown. Dr. Steele expressed concern that depression resulting from chronic illness (rather than straightforward Gulf War illness) could be responsible for the profile being presented by Syndrome 2 subjects. Drs. Sullivan and Steele

emphasized the need for larger, broader samples that extended beyond subjects classified within Syndrome 2. Dr. Haley answered that sample size wouldn't fix everything.

Dr. James O'Callaghan, a member of the Committee, then remarked on the dearth of evidence pointing to irreversible pathology. He asked if the findings point to any specific preclinical/treatment directions. Dr. Haley replied that the preclinical explorations remained broad with regards to multiple mechanisms.

Dr. Floyd Bloom, a member of the Committee, remarked on the difficulty of interpreting preliminary data. He added that, from what had been presented (hypervigilance, hyperarousal), he suspected involvement of the ascending reticular formation, locus coeruleus, and substantia nigra. He added that this could be tested by using alpha-2 agonists that might suppress the activity of the locus coeruleus. Dr. Hart then commented on the high levels of sleep disorders found in these ill veterans, another indicator that the locus coeruleus could be involved.

LTC Knox then brought up the Eli Lilly drug, Cymbalta, which has FDA approval for diabetic neuropathy and major depressive disorder. She then asked if there was any in-office procedure that could be used in place of the physostigmine challenge test. Dr. Haley replied that he did not know of any. Dr. Bloom commented that, for reasons unknown, there is a very good correlation between pupillary dilation and activation of the locus coeruleus. Dr. Haley responded that his autonomic battery involves assessing pupillary dilation.

LTC. Knox then asked Dr. Haley to review the characteristics of Syndrome 4. Dr. Haley said that he could not recall it at the present time.

Dr. Bill Meggs then reflected that the best described organophosphate (OP) chronic disability in humans, organophosphate induced delayed neuropathy (OPIDN), is described as an axonopathy and not a myelinopathy. He asked Dr. Haley how that fits into the data from the UTSW research. Dr. Haley replied that, over time, the peripheral neuropathy recovers but that the central neuropathy does not. Dr. Golomb remarked that GWI was not caused by OPIDN. Dr. Haley then commented on the phenomenon of "promotion," whereby carbamates – if given after organophosphate exposure – can accelerate the process of axonopathy. Dr. Meggs added that not all OPs act or clinically manifest in the same way.

Chairman Binns then reflected on the need for clear criteria by which Dr. Haley and the UTSW research team can select which batteries should be used in broad GWI diagnoses. He found particular value in those tests which are robust, can easily be used in VA hospitals, do not pose safety or ethical concerns, and do not depend on subject compliance. Chairman Binns remarked that he felt the need for tests to be based on subjects outside the Syndrome 2 group (e.g. based on subjects without high rates of psychiatric disorders, including depression).

At 3:40pm Chairman Binns called for a 10 minute break.

The meeting reconvened at 3:50pm.

Preclinical Studies Discussion

Chairman Binns called for Dr. Haley to proceed with updating the Committee on the status of the UTSW preclinical study research.

Dr. Haley then presented an overview of the preclinical studies (Appendix – Presentation 23). Dr. Haley stated that the trials were originally going to be funded for 2 years, but this timeframe was shortened to a 1 year maximum for initial “feasibility” trials.

Dr. Meggs asked which organophosphates that the UTSW group was studying. Dr. Haley said that the 1st phase included chlorpyrifos, pyridostigmine bromide (PB) and sarin.

Chairman Binns then called for questions.

Dr. O’Callaghan asked Dr. Haley if he planned to have a dosing meeting to go over his protocols. Dr. Haley replied that the dosing meeting would not include all preclinical study investigators and would include only those whose research was relevant to the discussions. He added that at the end of the 3rd quarter, the Merit Review Group (MRG) would be meeting with the research groups. Dr. Haley then stated his difficulties with the contracting process for his continued funding.

Dr. Steele asked if these contracting constraints would prevent the UTSW team from looking at the persistent and delayed effects of OPs (6-12 months out), as previously requested by the Committee. Dr. Haley replied that the first (1 year) phase would not be able to accommodate these tests, but that subsequent research trials could. He further stated that, with the exception of a few studies, the early investigations will only look at exposure effects of 6 weeks or less. Dr. Steele also asked if any studies had been discontinued due to contracting issues. Dr. Haley replied that this had not occurred yet. Dr. Craig Powell, from the UTSW neurology department, remarked that at least 5 of the preclinical studies look at short and long-term exposures (3 months out).

Chairman Binns then asked Dr. Haley to focus on the UTSW responses to the Committee’s April 18, 2008 recommendations. Dr. Haley presented several of these responses and then answered related discussion questions (Appendix – Presentation 24).

Dr. O’Callaghan, who sits on the merit review group (MRG), expressed concern with the potential impact of the contracting process on the research. He remarked that he would like investigators not to be penalized for changing their research protocols after results from the initial (1 year) studies are obtained. Dr. Haley then proposed that the UTSW researchers get together, preview findings and draw up recommendations for the next research phase prior to meeting with the MRG. Dr. Steele then confirmed that Dr. O’Callaghan was requesting that Dr. Haley’s research team set guidelines establishing what constitutes the basis for continuing vs. discontinuing research protocols.

Dr. Haley then introduced Dr. Perry Adams, the Vice President for Research Administration at UTSW and a neuropharmacologist involved in overseeing the preclinical projects. Dr. Adams

told Dr. O'Callaghan and the Committee that he would like the UTSW preclinical investigators to meet no more than 9 months out, prior to the MRG review at 12 months.

Dr. Haley then continued with the UTSW responses to the RAC recommendations. In response to the DEET studies, Dr. Steele asked if Dr. Haley's earlier research (which found no effects from DEET) had used repeated low-dose exposures or not. Dr. Christopher Sinton replied that the original studies with repeated low-dose DEET exposures showed negative results, but that future studies are warranted. Dr. Sullivan added that several organophosphate pesticides (OP) other than chlorpyrifos could also be investigated since they were also used widely during the Gulf War. She stated that dichlorvos (used in pest-strips) was also widely used and should be considered in these models. She asked if this was a possibility for future studies. Dr. Sinton replied that grant applications were written and submitted to the Department of Defense (DoD) but that none had been accepted. Dr. Sullivan emphasized the importance of investigating the combination of pesticides, since 15 different acetylcholinergic acting pesticides were widely used during the Gulf War and have been identified as pesticides of concern by the Department of Defense' Environmental Exposure Report – pesticides (EER). Dr. Sinton agreed that the issue of synergism was important.

Chairman Binns continued with the Committee recommendations. Dr. Haley asked if the Committee really wanted the study of vaccine effects on immunologic function to be cancelled. Dr. Steele replied that the Committee's recommendation had been to look at the effects in the brain rather than the periphery, but not to cancel the study altogether.

Chairman Binns then asked Rev. Joel Graves, a member of the Committee, to share his personal experience with GW illness. Rev. Graves spoke about his troop's exposure to pesticides, burning oil fires, pyridogstigmine bromide, and other environmental toxins during the Gulf War. He described the problems he experienced upon returning from the war, including memory loss. He also commented on his intake of dietary supplements, namely lecithin and magnesium, which he believes boost his memory and general cognitive functioning. He said that over the past year or two his other symptoms, including pain, had improved as well. He then proposed that clinical trials using MRI be conducted on ill Gulf War veterans using these supplements.

Chairman Binns thanked Rev. Graves and commenced the Public Comments session.

Public Comments

Paul Sullivan was the first audience member to speak. As a GW veteran, Mr. Sullivan stated that he had helped force the DoD to admit that GW soldiers may have been exposed to chemical warfare agents. He spoke on behalf of ill GW veterans who want the Committee to forcefully request that the Secretary of Veterans Affairs review the VA-IOM contracts. He said that about 60 papers were omitted from the literature review conducted by the IOM, and that this was having a negative impact on research and research funding for GWI. Reading from page 158 & page 307 of the 2008 RAC Report, Mr. Sullivan accused IOM of blatantly violating the Persian Gulf Veterans' Act of 1998 by not considering findings from toxicological studies of animals when studying certain exposures. Mr. Sullivan concluded by thanking the Committee for holding

many meetings and working tirelessly on behalf of ill GW veterans. He also urged the Committee to be aware of the issues afflicting the Afghanistan and Iraq War veterans.

Dr. Peter Pressman thanked the Committee and remarked that some of the materials that the Committee had shed light on will enable clinicians (including himself) to care for the population of southern Iraq, particularly children ages 8-18 who are presenting with what amounts to an amplification of a number of GW illnesses. These illnesses include cognitive deficits of psychomotor slowing and other abnormal clinical symptoms.

Randy Stamm, a GW veteran suffering from GWI, then presented his anecdotal experience and volunteered himself for future research studies. Mr. Stamm also recommended that research be done on the soil surrounding oil well fires.

Kirt Love, a GW veteran and member of the VA Advisory Committee on Gulf War Veterans (a separate entity from the Research Advisory Committee), then spoke to the Committee. He mentioned that he has been advocating for a Gulf War clinical center for two years, and is also pushing for dietary treatment trials. He said that he has been told VA does not have the space for such a clinic, and he thinks that possibly it will need to be a more universal clinic to serve veterans of wars other than the Gulf War, including the Iraq War. He added that many veterans have lost faith in the VA system, and that this will complicate research and advocacy efforts. Mr. Love also mentioned that the VA had cancelled a recent meeting of his committee, and had asked for committee recommendations early, giving him concern that his committee would be wrapped up early, instead of going to the extended deadline of December. He emphasized that research and treatment are two separate entities, and that continued attention must be given to the treatment end of Gulf War illness.

Dr. Bill Goldberg, the Designated Federal Officer from VA, clarified that every federal advisory committee under the purview of VA is being reviewed and that the Advisory Committee on Gulf War Veterans' healthcare and benefits was not being singled out. Dr. Goldberg said that he had not received any notification regarding the cancellation of any committees.

Mr. Hood spoke about his experiences in the US Air Force during the Gulf War, and the medical care he has received as a veteran. He described the harsh environmental conditions and illnesses experienced by the GW veterans, including sandstorms and "hemorrhagic fevers" which caused bleeding from the lungs and other body parts. He described the process of having to write his own medical claim after his return from the Gulf War, and the difficulties he experienced getting medical consultations through the VA system. Mr. Hood detailed the numerous specialist doctors that he receives care from outside of the VA system. These include neurologists, pain/rehabilitation professionals, ear nose and throat doctors, cardiac doctors, pulmonary physicians, oncologists, and others.

Ms. Denise Nichols, a GW veteran and advocate, has been campaigning veterans and civilians to write letters to carry research forward. She also mentioned that some Saudi Aramco teachers that were in Iraq during the Gulf War currently suffer from symptoms of GWI. Ms. Nichols also commented on the undiagnosed illnesses of current troops deployed to Iraq and Afghanistan. She

also advocated for the creation of an online GWI Research Network. Ms. Nichols also suggesting that the Committee meet in Minneapolis in the future.

Chairman Binns then concluded the meeting for the day.

Day 2

Chairman Binns began the second day of the meeting at 8:15am with a brief review of the different case definitions used to determine the number of ill GW veterans (Appendix – Presentation 25). He specifically referred to a table found on page 26 of the recent RAC Report. In reviewing the findings, Mr. Binns expressed his concern that the survey questions inquiring about pain and fatigue were not standardized, and could greatly influence the study outcomes. He emphasized that small differences in the questions posed to veterans on surveys can make large differences in the percentages of veterans considered as “cases.”

Dr. Haley then presented a brief overview of the national UTSW survey of GW veterans before introducing the statisticians from Research Triangle Institute (RTI) International who are analyzing the UTSW survey data.

U.S. Military Health Survey (USMHS)

Mr. Vince Iannacchione, RTI International
Dr. Carla Bann, RTI International

Mr. Iannacchione and Dr. Bann spoke about the USMHS design and data collection procedures, provided an overview of some highlights from the preliminary findings of the military health survey, and compared current case definitions (Appendix – Presentation 26).

During Mr. Iannacchione’s presentation Dr. Golomb asked whether the number of call attempts used to reach each respondent were factored into the analyses. Mr. Iannacchione replied that this was accounted for in the adjustments made. [00:38:00]

2008 USMHS Correspondence Analyses

Dr. Mette Posamentier, University of Texas Southwestern

Dr. Posamentier presented the results of her exploratory analysis of the USMHS (Appendix – Presentation 27).

She explained that for the majority of the graphs, each dot represented a survey respondent. Dots to the left represented patients reporting the greatest number of symptoms asked about in the

survey (out of 371 total symptoms), while dots to the right represented patients reporting the least symptoms. Self-rated symptom severity was not represented in the graphs. Rather, the x-axis was a measure of the number of symptoms reported by survey respondents. The y-axis attempted to separate symptoms by “type” (somatic on one end, cognitive at the other). In the 2 graphs which list symptoms next to the plots, each dot represented a single symptom, and its lateral placement indicated how many “endorsements” it had (i.e. dots to the left indicated symptoms most commonly reported, while those to the right were least reported). Dr. Posamentier also noted that the numbers plotted on the “Factor” slides represented Syndromes 1-6.

During the presentation, Dr. Golomb expressed concern over what the “severity of symptoms” dimension (the x axis, labeled dimension 1 on Dr. Posamentier’s graphs) was actually measuring, since the plots were actually correlated with the *number* of veterans who reported suffering from each symptom rather than the individual veteran’s rating of symptom severity. She remarked that the graphs depicted which symptoms were most and least commonly reported among the veterans, according to their survey responses, but did not truly indicate symptom severity. Dr. Posamentier replied that survey respondents were asked to rate the severity of each symptom from 1-3 (1 being severe, 2 moderate, and 3 none/normal), but that these ratings were not yet included in any of the analyses. She added that symptoms reported by less than 5% of survey respondents were excluded from the analyses.

Survey & Case Definition Discussion

After Dr. Posamentier completed her presentation, Chairman Binns expressed concern that her method of classification excludes some patients with Gulf War Illness (namely those whose symptoms are not on the severe end of the spectrum). Dr. Haley commented that some method must be used to eliminate the noise or “background symptoms” from the case definitions. He argued that the correspondence analyses presented by Dr. Posamentier could help weed out veterans who might be ill due to causes unrelated to GWI. Dr. Golomb remarked that the Kansas definition uses exclusionary criteria and is highly effective at doing this, as demonstrated by its ability to distinguish symptomatic Gulf War from non-deployed era veterans. Drawing on information from Dr. Haley’s research and the RAC Report, Col. Knox, Chairman Binns and Dr. Steele remarked that Dr. Haley’s syndromes (and associated factor analyses) identify veterans who are sicker, but exclude some veterans with Gulf War illness whose symptoms are less severe. Dr. Golomb then warned about the dangers of inflating relative risk through selective analysis, and of conflating relative risk with attributable risk. Dr. Golomb was also concerned with the predominant focus on Syndrome 2, which is only representative of a subset of ill Gulf War veterans. She also stated that the findings represented in the correspondence analysis were reflective of Syndrome-based selection (e.g. veterans suffering from Syndrome 2 exhibit cognitive deficits by definition, otherwise they would not have met the syndrome criteria).

Chairman Binns brought up the concern that many of the veterans in Dr. Haley’s study suffer from depression, and that this is not representative of the general population of ill Gulf War veterans, as argued by Dr. Simon Wessely. Dr. Haley argued that the depression was caused by brain disease (e.g. white matter disease, multiple sclerosis), and that it should therefore not be a

disqualifying factor for Gulf War illness. Dr Haley argued that Dr. Wessely's study included individuals who probably were not suffering from war-related dysfunction. Dr. Haley and the Committee continued to debate whether his very high rates of depression were a confounding factor in his study.

Dr. Golomb suggested that Dr. Haley broaden his case definition to include veterans who meet other validated, highly discriminatory case definitions. Dr. Haley said that he wants to incorporate other case definitions (CDC and Kansas) but that he only wants to include cases that look like real illness.

Dr. Steele asked if Dr. Haley was concerned that the factors he identified in the deployed veterans were identical to those identified in the non-deployed veterans. Dr. Haley replied that this did not bother him, that he believes Gulf War illness also exists in the civilian world, particularly among members of the non-deployed military who may face similar exposures such as vaccines or pesticides.

Dr. Haley remarked that, regardless of the case definition used, there will always be some positive cases in non-deployed veterans.

Dr. Golomb commented that clusters of symptoms don't indicate syndromes. Dr. Meggs remarked that varied symptoms (affecting different organs) can represent one common illness. Dr. Meggs interpreted Syndrome 2 as Gulf War induced toxic encephalopathy, which is only one type of manifestation of illness resulting from complex mixtures of toxic exposures that occurred in the Persian Gulf during the war. He argued that these patients represent only a small subgroup of veterans with Gulf War Illness.

Dr. Golomb expressed concern that some of the patients who fit in the CDC and Kansas case definitions would be excluded by Dr. Haley's definitions, though she commented on the need for more discussion of Syndromes 3 and 4. Dr. Haley expressed his belief that Syndromes 1 and 3 could encompass many of these patients who have "disconnected" symptoms.

Dr. Golomb remarked that it would be useful if Dr. Haley's cases definitions were exportable, which would allow an outside party to analyze and compare all case definitions. When asked for her recommendation, Dr. Steele told Dr. Haley that the best way to define GWI would be to identify differentiating symptom patterns that are present in deployed veterans but have low prevalence in non-deployed Gulf War veterans.

Chairman Binns expressed concern that small changes in the survey questions asked by one group could dilute the end results, thereby underestimating the prevalence of disease. As an example, he mentioned that while Dr. Steele found a 4:1 risk ratio of GWI in deployed vs. non-deployed veterans, Dr. Haley's group found a 2:1 risk ratio when they used her case definition with their own modified survey questions. Dr. Haley asked what he would recommend for questions, and Chairman Binns replied that the ideal solution would be to start the survey over. Dr. Golomb added that the study should include people who meet the Kansas definition.

Dr. Steele expressed concern with Dr. Haley's survey methodology, which differed from other surveys in question content and evaluation of symptom severity.

Dr. Steele also remarked that looking at symptom clusters based on exposure might result in very different case definitions and syndrome groups.

Dr. Golomb suggested the possible utility of analyzing survey data with unsupervised neural networks, which would allow multi-dimensional analysis, self clustering of groups, and could include exposure and symptom criteria. Dr. Posamentier replied that the correspondence analyses are multidimensional.

Drs. Steele and Golomb then agreed that the factor/syndrome analysis approach being used by Dr. Haley doesn't help define GWI. Rather, it is self-selecting in that it confirms that people with more symptoms are more likely to have those types of symptoms. Dr. Haley argued that his study defines subgroups of GWI, and that his studies have used brain imaging to identify different activation patterns in each syndrome group. Dr. Golomb replied that she was not disputing the fact that people exhibiting different patterns of symptoms may present different brain imaging results, but that she was concerned about excluding a broad mass of people who don't fit into Dr. Haley's Gulf War Illness syndromic definitions.

Dr. Steele then made the point that she could take the same data set and run multiple factor analyses in different ways and come up with different results, and that subsetting the population in different ways would also produce different results. Dr. Haley denied that this was true.

Chairman Binns then called for a short break.

At 11:21am Chairman Binns reconvened the session. Dr. Carrolee Barlow, a member of the Committee, called in via conference phone for this session of the meeting.

Chairman Binns began the session by calling for comments from those who had not had a chance to speak.

Dr. Bloom stated that everything he has learned about Gulf War Illness has been through Committee hearings. He remarked that there appears to be an intrinsic assumption that there is only one Gulf War Illness, but that the initial results from Dr. Haley's studies appear to have identified a subset of those who may have a particular syndrome for which enough of the mechanism could be understood to develop a treatment trial. He added that it would be highly difficult to identify a single treatable cause in all ill GW veterans. Dr. Bloom suggested that when individuals are brought in for Phase 3 of the clinical trials at the hospital they should also be administered the Kansas survey questionnaire. This information could be used to determine whether the group selected for the clinical trial (Syndrome 2 patients) included or excluded people matching the Kansas criteria. Dr. Bloom added that the nature of the sleep problems that many of the GW veterans with depression are reporting need to be evaluated.

Chairman Binns remarked that he and Dr. Steele had spoken over the break about the idea of resampling subjects with the Kansas questionnaire as they come in for the study, and Dr. Steele

expressed some concern that this method could miss patients with GWI who were originally screened out of Dr. Haley's syndromes.

Dr. Sullivan then asked if Dr. Haley was using any exclusion criteria for his factor/syndrome groups. Dr. Haley replied that the imaging studies exclude anyone with other diseases or injuries affecting the brain, such as stroke, ALS, and MS.

Dr. Sullivan also remarked on the high rate of self-reported continuous shaking, and asked what the exact survey question pertaining to this symptom was. Dr. Haley replied that, in addition to asking if subjects had a doctor's diagnosis of Parkinson's disease (only 3 did), the survey asked, "Do you have continuous shaking in any part of your body? (If so, is it in the upper, lower extremities, left/right side?)" 600 respondents reported having this symptom, and it was more common in people under age 50 than those above age 50, and 3 times more common in the deployed than in the nondeployed veterans. Dr. Haley added that the symptom report of continuous shaking is 8 times more common in people with Syndrome 2 than everyone else, 6 times more common in Syndrome 1, and 2 times more common in Syndrome 3.

Dr. Barlow then said she agreed with Dr. Bloom. She pointed out that doing clinical trials for efficacy, which is the first step to bringing treatments to ill Gulf War veterans in general, requires a homogeneous group. Dr. Barlow expressed concern, however, that the clinical trial definitions might get used more broadly in the context of defining GWI. She recommended implementing a strategy that makes it clear that a much more narrow definition is being used for the purpose of clinical trials, but that this definition does not reflect the Committee's overall feeling of what GWI actually is.

Dr. Golomb, having spoken with Dr. Haley over the break, mentioned their agreement that new/different questions or biomarkers might help elucidate patterns among ill GW veterans whose symptoms appear disaggregated in the current factor analyses. Dr. Golomb also expressed the concern that Dr. Haley's syndromes appear to be symptom manifestations, and not necessarily representative of underlying pathogenesis. She further explained that this was exemplified by some "Syndrome 1" patients becoming "Syndrome 2" over time. Dr. Haley agreed that this was yet to be determined.

Col. Knox asked if this same shift was occurring in Syndrome 4. Dr. Haley replied that this was possible, since more subjects met the criteria for Syndrome 4 in the recent study than in the original 1997 study. Dr. Haley agreed with Dr. Golomb that a common etiology might underlie the different syndromes and manifest differently in different individuals over time.

Chairman Binns wrapped up the morning session by stating that the research summed up in the RAC Report found twice the prevalence of GWI in deployed veterans than identified by Dr. Haley's research.

UTSW Sampling Update

Dr. Robert Haley, University of Texas Southwestern

Dr. Haley presented the status and future sampling plans for the survey, neuroimaging and biomarker, and the blood specimen studies (Appendix – Presentation 28).

Regarding options for the national survey study, Dr. Bloom suggested concentrating on tracking down missing twins in the proposed effort to conduct field follow-up of non-respondents. Dr. Haley and Mr. Iannacchione agreed that this was a good idea, and asked if any other Committee members had additional thoughts.

Dr. Steele raised the point that although the sampling weight adjustments can address whether or not the sample is representative in terms of demographics or location, doing so cannot indicate whether the sample is representative in terms of health characteristics. She added that the large VA survey looked at whether their survey was biased based on health characteristics, such as by investigating whether sicker GW veterans were more likely to participate than healthier GW veterans. The VA survey assessed this by conducting a field follow-up of non-respondents, asking key questions about their health in brief interviews. Dr. Steele was particularly interested in knowing more about the non-deployed veterans who did not respond, as well as those who refused to participate. Mr. Iannacchione agreed with this approach, though noted that Institutional Review Board (IRB) rules prohibit re-contacting individuals once they refused to participate.

Chairman Binns then asked for an update on the twin study. Dr. Haley said he had just received the data, that 96 pairs were complete, and that he did not yet know how many are discordant for his syndromes. Drawing on Dr. Bloom's suggestion, Chairman Binns proposed that all twins be re-surveyed with the exact Kansas definition when they come in for testing. Chairman Binns asked if any of the planned re-sampling work could address the concerns raised by the Committee regarding the survey questions. Dr. Haley and Mr. Iannacchione replied that the three "reserve samples" could be extrapolated to the general population, either independently or in combination. Mr. Iannacchione added that a new questionnaire could be given to these samples as well, to investigate if the subjects meet CDC and Kansas definitions.

Dr. Haley then proceeded to discuss the sampling plan for the neuroimaging study. The main question he posed to the Committee was whether they recommended adding another group, representative of the Kansas definition, to the study. Dr. Steele replied that a much larger sample was needed in order to accurately tease out patterns of exposure and the various clinical manifestations. Dr. Bloom recommended conducting full analyses on all study participants, and using these results to draw out the most informative imaging and psychological test combinations. Dr. Haley replied that it would be difficult to narrow down the testing methods since the vast majority seem to be useful, based on initial results. Dr. Barlow noted that she believed the Committee was only requesting that tests in the neuroimaging component be pared down. She also asked how Robert was calculating his power calculations. Dr. Steele cautioned that the proposed sample size (100 independent subjects plus 160 monozygotic twins) was still too small. Dr. Sullivan asked if the sample size could be doubled. Dr. Haley replied that more money and time would be needed. Chairman Binns commented that Dr. Haley's groups must be

looked at as a subset of GWI, but that this is in conflict with the overall goal of elucidating the pathogenesis of GWI more generally. Dr. Barlow added that if the aim of the study is diagnostic, rather than tracking treatment, Dr. Haley needs far more subjects because patients can serve as their own controls in treatment trials but not in diagnostic trials. Dr. Haley argued that his studies are pre-diagnostic and pre-therapeutic in that they are still trying to understand the nature of GWI. Chairman Binns asked Dr. Haley to maintain consistent goals, commenting that Dr. Haley's external committee seemed to believe his research is aimed at developing diagnostic tools, since they advised him to pare down his studies to determine which ones were more likely to be useful in diagnosing GWI.

Reading from the Committee's written recommendations for the UTSW program, Chairman Binns remarked that Dr. Haley had intended to conduct pilot studies in Navy Seabees and twin pairs, but that now he did not have enough twins to do so. Dr. Haley replied that the original plan was to conduct pilot studies in the Seabees first, and then either to proceed with independent subjects *or* the twins. Chairman Binns recommended that Dr. Haley find more twins in order to fulfill his originally proposed study design.

Dr. Haley finished the session by providing a sampling update for the blood/DNA study. Dr. Barlow and Dr. Steele recommended including as many controls as possible, for genomic and other reasons. Dr. Barlow added that doing so would also provide an opportunity to look at resiliency factors.

General Recommendations

Chairman Binns conducted a review of UTSW's responses to several of the Committee's general findings and recommendations from the UTSW review document.

Chairman Binns began by confirming that Dr. Haley plans to create an expert panel that will include several people from the Research Advisory Committee as well as external experts with a background in Gulf War illness research. He then asked Dr. Haley about the request made by UTSW's external advisory review committee that there be an integration of the research data into a uniform fMRI data processing module. Dr. Haley agreed this was a critical part of the plan, but that it was not yet developed. Chairman Binns suggested discussing Recommendation 5 at the next Committee meeting in June. He then reviewed Recommendations 6 and 7. Dr. Haley stressed that collaborating with the VA to develop a model and establish a clinic for evaluating and treating ill Gulf War veterans was essential, though the VA had not yet expressed enthusiasm about doing so. Chairman Binns followed up by asking about Recommendation 8, and the challenges of implementing such a plan in a system that lacks a mechanism to do so. Dr. Haley replied that inherent bureaucracy and contract problems were the greatest hurdle. He added that after meeting with the head General Council and head contracting people 6 months earlier, the Veterans Integrated Service Network (VISN) appointed a program manager who is working on streamlining the contracting process. Chairman Binns thanked Dr. Haley and the UTSW research team, and expressed his hope that the data produced from the neuroimaging and survey studies would be exportable and useful to other researchers interested in studying GWI in diverse ways, beyond Dr. Haley's selected sub-groups. Dr. Haley responded by thanking the

Committee for the frank discussion. Dr. Steele asked if this discussion would be continued at the next meeting and Chairman Binns confirmed that this would be necessary.

Public Comments

Mr. Randy Stamm, an ill GW veteran who takes 63 pills every day, offered to share photographs of oil well fires taken during his service. He also asked why a liaison from the Dallas VA was not present at the meeting. Mr. Stamm went on to express frustration with the VA disability compensation procedures. Chairman Binns reminded Mr. Stamm that the Committee is only charged with research-related issues, but that there is another committee (the Gulf War Veterans Advisory Committee) dealing with benefits and clinical care issues. Mr. Stamm requested the scope of studies be broadened to include more veterans. He also mentioned that non-deployed veterans involved in loading planes in the United States during the Gulf War may also be sick.

Mr. Hood, a Gulf War veteran, encouraged researchers and clinicians to conduct tiered mycoplasma series, Epstein-Barr, stealth virus, and other blood tests on Gulf War veterans.

Mr. Mark Anderson, a journalist with the American Free Press, asked the Committee to keep depleted uranium on the table, in terms of research and treatment. He also advocated for dietary and alternative treatment trials to be explored. Mr. Anderson also expressed his belief that the current conflicts in Iraq and Afghanistan need to be brought into the fold at some point. Lastly, he urged everyone in the room – as American citizens – to work toward a non-interventionist foreign policy.

Maj. Denise Nichols, a Gulf War veteran and nurse, thanked the Committee and asked current and future surveys to include questions about all diagnosed illnesses veterans are experiencing. She also asked the Committee to consider ocular, dental, and bone diseases as well.

At 1:25pm, Dr. Steele thanked the veterans for coming, and concluded the meeting by noting that the current date was the 18-year anniversary of the beginning of the ground war in the Persian Gulf.