Research Advisory Committee on Gulf War Veterans' Illnesses

July 18-19, 2007, Committee Meeting Minutes

Dallas, Texas

DEPARTMENT of VETERANS AFFAIRS

Research Advisory Committee on Gulf War Veterans' Illnesses
VA Eastern Kansas Healthcare System (T-GW)
2200 S.W. Gage Blvd. Topeka, KS 66622

I hereby certify the following minutes as being an accurate record of what transpired at the July 18-19, 2007, meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses.

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

Table of Contents

Attendance Record 5

Abbreviations 6

Welcome, introductions, and opening remarks 11

Chronic Fatigue Syndrome / Myalgic Encephalomyelitis (CFS/ME): a disease characterised by neuro-immune features and virus infection 11

Gulf War Illness and Chemical Exposure Research Program at University of Texas Southwestern Medical Center, Dallas: Implementation of the Research Recommendations of the VA RAC-GWI 17

Neuroimaging Introduction and Overview 18

Gulf War Illness Neuroscience Projects Overview 18

Testing Hypotheses of Changes in Prefrontal Function Related to Gulf War Syndrome 19

Fronto-Striatal Systems in Depression and Gulf War Illness 20

Conjunction Memory Paradigm: Preliminary Data 20

EEG Program for Gulf War Research 20

MR Spectroscopy at 3T 21

DTI Sub-Core: Imaging Protocol and Prelim Data 21

Perfusion and Regional Cerebral Blood Flow (rCBF) Using MRI Arterial Spin Labeling (ASL) 21

Committee discussion – Day 1 21

Public Comment – Day 1 28

Day 2 31

MRI Reveals Evidence of Structural Brain Differences Among Veterans Deployed to the first Gulf War 31

Environmental Medicine and Gulf War Illnesses: Does the map fit the territory? 35

Update on Research in Persian Gulf War Veterans Illnesses 37

2007 RAC Report: Discussion of Recommendations 38

Update on VA Gulf War research programs 45

Public Comment – Day 2 ..... **47**

Appendix **51**

Presentation 1 – Jonathan Kerr *51*

Presentation 2 – Robert Haley *76*

Presentation 3 – Richard Briggs *101*

Presentation 4 – John Hart, Jr. *103*

Presentation 5 – Michael Motes *119*

Presentation 6 – Wendy Ringe *136*

Presentation 7 – Jim Bartlett *151*

Presentation 8 – Thomas Ferree *170*

Presentation 9 – Sergey Cheshkov *177*

Presentation 10 - Roddy McColl *184*

Presentation 11 – Richard Briggs *193*

Presentation 12 – Roberta White *201*

Presentation 13 – Bill Meggs *212*

Presentation 14 – Beatrice Golomb *264*

Presentation 15 – Lea Steele *293*

Attendance Record

Members of the Committee
James H. Binns, Chairman
Carrolee Barlow
Floyd Bloom
Beatrice A. Golomb
Anthony Hardie
Marguerite Knox
William J. Meggs
Mary D. Nettleman
James P. O'Callaghan
Steve Smithson
Lea Steele
Roberta White

Committee Consultant
Jack Melling

Committee Staff
Laura Palmer

Designated Federal Officer
William Goldberg

Guest Speakers
James Bartlett
Richard Briggs
Sergey Cheshkov
Thomas Ferree
Robert Haley
John Hart
Jonathan R. Kerr
Roddy McColl
Michael Motes
Wendy Ringe

Abbreviations

AChE	Acetylcholinesterase
ACTH	Adrenocorticotropic hormone
AFIP	Armed Forces Institute of Pathology
ALS	Amyotrophic lateral sclerosis
ASL	Arterial spin labeling
ATSDR	Agency for Toxic Substances and Disease Registry
CCEP	Comprehensive Clinical Evaluation Program
CDC	U.S. Centers for Disease Control and Prevention
CDMRP	Congressionally Directed Medical Research Programs
CEO	Chief executive officer
CFS	Chronic fatigue syndrome
CoQ10	Coenzyme Q10
CRADO	Chief Research and Development Officer (VA)
DFO	Designated federal officer
DOD	U.S. Department of Defense
DTI	Diffusion tensor imaging
EEG	Electroencephalogram
EPA	U.S. Environmental Protection Agency
ERP	Event-related potential
FDA	U.S. Food and Drug Administration
fMRI	Functional magnetic resonance imaging
FY	Fiscal year
GAO	U.S. Government Accountability Office
GWVIRP	Gulf War Veterans' Illnesses Research Program (DOD - CDMRP)
GWVIS	Gulf War Veterans' Information System
HPA	Hypothalamic-pituitary-adrenal axis
IDIQ	Indefinite delivery, indefinite quantity
IOM	Institute of Medicine
LHON	Leber's hereditary optic neuropathy
MCS	Multiple chemical sensitivity
MEG	Magnetoencephalography
Mn-SOD	Manganese superoxide dismutase
MRI	Magnetic resonance imaging
MPSS	Massive parallel signature sequencing
MRS	Magnetic resonance spectroscopy
MS	Multiple sclerosis
mtDNA	Mitochondrial DNA

NIH	National Institutes of Health (US)
OEF	Operation Enduring Freedom
OIF	Operation Iraqi Freedom
OPHEH	Office of Public Health and Environmental Hazards (VA)
ORD	Office of Research and Development (VA)
PB	Pyridostigmine bromide
PCR	Polymerase chain reaction
PTSD	Posttraumatic stress disorder
RAC-GWVI	Research Advisory Committee on Gulf War Veterans' Illnesses
RFA	Request for applications
ROS	Reactive oxygen species
SNP	Single nucleotide polymorphism
SPECT	Single photon emission computed tomography
UBO	Unidentified bright objects
UC Irvine	University of California at Irvine
UK	United Kingdom
UTSW	University of Texas Southwestern School of Medicine
VA	U.S. Department of Veterans Affairs

Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses
July 18-19, 2007

Wednesday, July 18: Meeting Held in Simmons Biomedical Research Bldg (NIB), Room 11.120
University of Texas Southwestern School of Medicine
6000 Harry Hines Blvd. (North Campus)
Dallas, Texas

[Please Note: The meeting will be held in a different location Thursday, July 19]

Wednesday, July 18
Agenda

8:00 – 8:30	**Informal gathering, coffee**	
8:30 – 8:35	**Welcome, introductory remarks**	**Jim Binns, Chairman** **Res Adv Cmte Gulf War Illnesses**
8:35 – 10:05	**Research on Chronic Fatigue Syndrome (CFS): a disease characterized by neuroimmune features and virus infection**	**Dr. Jonathan Kerr** **St. George's University of London**
10:05 – 10:20	**Break**	
10:20 – 12:00	**University of Texas Southwestern (UTSW) School of Medicine Gulf War Illness Research Program**	**Dr. Robert Haley** **Univ. of Texas Southwestern School of Medicine**
12:00 – 1:00	**Lunch**	
1:00 – 1:30	**UTSW Gulf War Research: Neuropsych testing, neuro projects, and research on word retrieval and emotional memory circuits**	**Dr. John Hart** **Univ. of Texas at Dallas**
1:30 – 2:00	**UTSW Gulf War Research: Studies of attention and executive function**	**Dr. Bart Rypma** **Univ. of Texas Southwestern School of Medicine / Univ. of Dallas**
2:00 – 2:30	**UTSW Gulf War Research: Frontostriatal systems in depression and Gulf War illness: Material-specific memory in the medial temporal lobes**	**Dr. Wendy Ringe** **Univ. of Texas Southwestern School of Medicine**
2:30 – 3:00	**UTSW Gulf War Research: Visual-auditory memory conjunction**	**Dr. James Bartlett** **Univ. of Texas at Dallas**
3:00 – 3:15	**Break**	

Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses
July 18-19, 2007

Wednesday, July 18: Meeting Held in Simmons Biomedical Research Bldg (NIB), Room 11.120
University of Texas Southwestern School of Medicine
6000 Harry Hines Blvd. (North Campus)
Dallas, Texas

[Please Note: The meeting will be held in a different location Thursday, July 19]

Wednesday, July 18
Agenda (cont.)

3:15 – 3:20	**UTSW Gulf War Research: Introduction and overview of neuroimaging studies**	**Dr. Richard Briggs** **Univ. of Texas Southwestern School of Medicine**
3:20 – 3:35	**UTSW Gulf War Research: Electroencephalography and electrical impedance tomography**	**Dr. Tom Ferree** **Univ. of Texas Southwestern School of Medicine**
3:35 – 3:45	**UTSW Gulf War Research: Magnetic resonance spectroscopy**	**Dr. Sergey Cheshkov** **Univ. of Texas Southwestern School of Medicine**
3:45 – 3:55	**UTSW Gulf War Research: Diffusion tensor imaging**	**Dr. Roderick McColl** **Dr. K.S. Gopinath** **Univ. of Texas Southwestern School of Medicine**
3:55 – 4:05	**UTSW Gulf War Research: Perfusion and regional cerebral blood flow (rCBF) using MRI arterial spin labeling (ASL)**	**Dr. Richard Briggs** **Univ. of Texas Southwestern School of Medicine**
4:05 – 4:10	**UTSW Gulf War Research: Image registration**	**Dr. Nasser Kehtarnavaz** **Ali Gholipour** **Univ. of Texas at Dallas**
4:10 – 5:00	**Discussion regarding University of Texas Southwestern School of Medicine Gulf War Illnesses Research Program**	**Committee**
5:00 – 5:30	**Public Comments**	

Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses
July 18-19, 2007

Thursday, July 19: Meeting Held at the Hilton Anatole
2201 Stemmons Freeway
Dallas, Texas

Thursday, July 19
Agenda

8:00 – 8:30	**Informal gathering, coffee**	
8:30 – 9:10	**Magnetic Resonance Imaging (MRI) reveals evidence of structural brain changes in Gulf War veterans**	**Dr. Roberta White** **Boston University School of Public Health**
9:10 – 10:30	**Environmental Medicine and Gulf War Illnesses: Does the Map Fit the Territory?**	**Dr. William Meggs** **East Carolina University School of Medicine**
10:30 – 10:45	**Break**	
10:45 – 11:30	**Update on recently published research relevant to the health of Gulf War veterans**	**Dr. Beatrice Golomb** **University of California at San Diego School of Medicine**
11:30 – 12:00	**Committee business: Report discussion and update**	**Dr. Lea Steele** **Res Adv Cmte Gulf War Illnesses**
12:00 – 1:00	**Lunch**	
1:00 – 1:15	**University of Michigan conference on multisymptom illnesses**	**Dr. Daniel Clauw** **University of Michigan School of Medicine**
1:15 – 1:45	**Update on VA Gulf War research programs**	**Dr. Bill Goldberg** **VA Office of Research and Development**
1:45 – 2:15	**Public comments**	
2:15	**Adjourn**	

The July 18-19, 2007, meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses was held on July 18 in Room 11.120 of the Simmons Biomedical Research Building (NIB) at the University of Texas Southwestern School of Medicine, 6000 Harry Hines Blvd., Dallas, Texas. On July 19 the meeting was held at the Hilton Anatole, 2201 Stemmons Freeway, Dallas, Texas.

Welcome, introductions, and opening remarks

James H. Binns, Jr. Chairman

Chairman James Binns called the meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses (hereinafter referred to as the "Committee") to order at 8:30 a.m. He welcomed Committee members, visiting scientists, Department of Veterans Affairs (VA) staff, and members of the public. He noted that the most recent VA study had found 175,000 Gulf War veterans, or 1 in 4 who served, are ill with chronic multisymptom illness. He extended special thanks to the ill veterans who were attending as Committee members and members of the audience. They remind us that this is not an abstract, scientific topic bringing us together. The transcending reality is that these 175,000 veterans were injured while serving their country in wartime. He also extended particular thanks to Dr. Robert Haley and his colleagues from the University of Texas Southwestern School of Medicine (UTSW) for inviting the Committee and members of the public to visit their campus that day. He also thanked them for undertaking the important task of understanding, and ultimately solving this problem.

Chairman Binns noted that Dr. Daniel Clauw was not able to attend the meeting because the University of Michigan had just been awarded a large National Institute of Health (NIH) clinical and translational sciences research grant. Dr. Clauw is the principal investigator on this project, and was required to attend meetings related to this project. He would therefore not be able to present an overview of the University of Michigan's conference on chronic multisymptom illness, as he was scheduled to do so the following day. Chairman Binns stated that, in light of this, his intention was to continue Thursday's meeting without a lunch break. This should allow the Committee to adjourn the meeting at 1:00 p.m.

Chairman Binns introduced the meeting's first speaker, Dr. Jonathan Kerr. Dr. Kerr is the director of a chronic fatigue syndrome (CFS) research program at St. George's in London. The program includes the development of a diagnostic test using mass spectroscopy and elucidation of CFS pathogenesis through analyses of gene expression. Chairman Binns noted that Dr. Kerr and his five colleagues were engaged and committed to the task with respect to CFS that UTSW had undertaken with respect to Gulf War illnesses. Chairman Binns was certain that attendees would find Dr. Kerr's research program impressive, including the fact that it had been accomplished on a total budget to date of 1 million pounds, or 2 million U.S. dollars.

Chronic Fatigue Syndrome / Myalgic Encephalomyelitis (CFS/ME): a disease characterised by neuro-immune features and virus infection

Jonathan R Kerr MD, PhD
Sir Joseph Hotung Clinical Senior Lecturer and Honorary Consultant in Microbiology
Dept. of Cellular & Molecular Medicine, St George's University of London, U.K.

Dr. Kerr presented an overview of his group's CFS research, which was focused on elucidating a gene expression signature, the role of virus infection in the ongoing disease, as well as identifying protein biomarkers. (See Appendix – Presentation 1.) Their research indicates that there are genetic subtypes among CFS patients, reflected by different genetic expression profiles.

Following Dr. Kerr's presentation, Dr. Carrolee Barlow, a Committee member, asked if the data from the massive parallel signature sequencing (MPSS) indicated higher or low levels of a particular viral genome. Dr. Kerr stated it provided a signature sequence for the entire genome. Dr. Barlow wondered if this data could help determine what was causative versus predisposing. She raised the question because gelsolin mutations are known to predispose to amyloidosis. One may be able to go in and determine if the identified differences were due to gelsolin gene expression differences. This might "pull out" the patients who are predisposed to CFS because they have an underlying gelsolin abnormality. She asked whether the resolution of the MPSS could reveal this. Dr. Kerr stated that there were not enough data to make this determination. He was getting ready to submit a grant proposal to look at differential expression of several of the target genes identified, and single nucleotide polymorphisms (SNPs) in general. Dr. Barlow asked if Dr. Kerr was planning to look at the whole genome or simply at variants in the genes already identified by MPSS. Dr. Kerr stated that they would be looking at variations in each of the identified genes.

Dr. Mary Nettleman, a Committee member, asked if Dr. Kerr could expound more on the "novel" virus that they had identified as possibly playing a role in CFS, as well as how they had characterized it. Dr. Kerr replied that they were currently conducting real-time polymerase chain reaction (PCR) tests, as well as regular PCR, to detect the presence of these markers. Dr. Nettleman asked if "novel" meant the virus was previously unknown or known, but not known to cause this disease. Dr. Kerr stated that it was a known mammalian virus, but preferred not to reveal more detail about its specifics.

Dr. Floyd Bloom, a Committee member, noted that Dr. Kerr's geographical distribution findings were very striking. This led back to Dr. Barlow's point: Are vulnerabilities or specific causative agents being revealed? Dr. Bloom asked if Dr. Kerr had plans to go back and look at family members from the same regions to see if the general population showed some of these characteristics. Dr. Kerr stated that they had identified family members and did have plans to investigate this aspect more. Dr. Barlow stated this was a key question to address. If there is a genetic predisposition to developing CFS, the controls must be a very different cohort. Models are available to evaluate affected family members and unaffected family members. Dr. Kerr agreed with this assessment.

Dr. Nettleman asked how Dr. Kerr's CFS research might relate to Gulf War illnesses. Dr. Kerr stated that there were significant overlaps between CFS and Gulf War illnesses. He noted that there were a lot of autonomic problems documented in CFS. His group hopes to look at gene expression in ill Gulf War veterans to determine the similarities and differences with their CFS patients. Dr. Nettleman stated that it has always struck her, with respect to Gulf War illnesses, that it affected such a large male cohort. This is unusual and generally a marker that "something is going on." There are also genetic correlations with gender and different proteins. She suggested this might be a focus for Dr. Kerr's future research. Dr. Kerr noted that one of their CFS subtypes was predominantly male.

Dr. Golomb commented that it would be interesting to see if ill Gulf War veterans were more likely to have variation in genes that might be involved in mitochondrial function. She stated that some studies have suggested that some immunological characteristics of non-Gulf War CFS patients differ from ill Gulf War patients. This may relate to the subgroup profiles, perhaps relating to groups that are more common in non-Gulf War veterans, or related to environmental exposures. Discussion followed about transcription factors that appeared to be down- and up-regulated in these patients.

Dr. Barlow asked if Dr. Kerr had ever performed the analyses in the opposite direction, i.e., identifying which clinical subtypes cluster together. Dr. Kerr stated that they had done this analysis. Dr. Barlow asked if they had been able to identify subgroups, not based on the genes differentially expressed, but across all CFS characteristics. It might be worthwhile to see if groups really stand out as being different.

It might also answer Dr. Golomb's question, i.e., if two groups stand out and one has a higher incidence in males, this might help understand the difference between Gulf War syndrome clusters and the CFS clusters. Dr. Golomb noted that there are occupational differences in men and women. Some of the occupations that involve more toxic exposures commonly involve men. Dr. Nettleman commented that symptom expression profiles are quite varied in the Gulf War population as well.

Dr. Steele, a Committee member and scientific director, thought it was remarkable that Dr. Kerr was able to identify gene subtypes that were highly correlative with symptom and severity types in different realms. She thought it was important to determine how the subtypes correlated with triggering events or exposures. Dr. Kerr's studies showed gene expression that varied on a geographical basis. It would be interesting to see if the agricultural community subtype was more common in the ill Gulf War veterans, for example, and then see if this correlated further with severity or symptom profiles. It would be of interest to tease out etiologic factors for the illness with these subtypes.

Dr. Steele asked if Dr. Kerr's group had been able to characterize the subtypes in a descriptive way, e.g., that a group had upregulation of X, down regulation of Y, etc. Dr. Kerr replied that they had just gotten some screening data on this and were planning to analyze the data. Dr. Golomb noted that the issue remained as to how much was related to vulnerability and how much was related to the effects of chemicals on DNA expression. Dr. Barlow cautioned Dr. Kerr that, while it was great to do the clustering, he should also do a more unbiased approach to find unique signatures. Dr. Kerr stated that he was aware of this concern. He stated that he believed this was a heterogeneous disease.

Dr. Bloom asked Dr. Kerr to speak a little about the natural history of CFS, in particular the age of onset and prognosis for natural recovery. Dr. Kerr stated that the CFS population included children, adolescents, and adults up until 60-or-70-years-of-age. Six months of disease is required for diagnosis, and people can spontaneously remit but generally don't get back total function. They may become sick again with other stressors. Dr. Golomb commented that some do stabilize and recover, but others remain ill. Dr. Steele added that, like Gulf War illness, the percentage of those who recover was relatively low, while a smaller percentage fully recovers.

Mr. Anthony Hardie, a Committee member, asked if the "novel" virus infections were triggers or unrelated to symptoms and perhaps opportunistic. Dr. Kerr stated this wasn't understood yet. Dr. Golomb stated that it was a good point that the viral infection may be opportunistic. It may potentiate the illness, but may not be a primary etiological factor. Dr. Kerr stated that it could also be the other way. We just don't know. Dr. Steele asked if Dr. Kerr would be testing for the "novel" virus in his Gulf War patients. Dr. Kerr stated that he would.

Dr. Haley, director of the UTSW Gulf War research program, commented that the heterogeneity of these patients was the most interesting part in this challenge. When this is solved, they will probably find homogeneity factors within the subgroups. So how the subgroups are derived is critical. Dr. Kerr stated that he hadn't shown the original clustering data. Basically they clustered the relative quantities of each of the 89 genes in all of the CFS patients. Dr. Haley stated that this was a problem that he had been interested in for 15 years. He noted that there are numerous ways to look for subgroups, e.g. cluster and factor analysis, etc. Many, like Dr. Haley, use factor analysis. However, the first time one does the analysis; it probably doesn't make much difference. The advantage of factor analysis is that once the factors are identified, there is a mathematical description of these factors that can be applied *a priori* in another group. But cluster analysis requires that the clusters be derived *de novo* every time. Dr. Haley thought Dr. Kerr may have something here, and suggested that he go back and redevelop these groups as factors. Dr. Kerr could then apply the factor weights in his next study and create the same groups with

the same mathematical definitions. This would allow him to test hypotheses instead of redefining the sample variation.

Dr. Golomb stated that the opposite viewpoint was that one should not use factor groupings that might have been specific to one's sample and analysis. Dr. Haley agreed that one's initial study might generate spurious findings but that doing this research multiple times in multiple groups, one would hope to arrive at some factors that do replicate. This does not happen with cluster analysis. One can not perpetuate a cluster. Dr. Haley stated that Dr. Kerr's data were objective measures and could provide great building blocks for establishing factors. Cluster analysis is an exploratory approach in his opinion. Now that the evidence indicates that something is going on, one should go back and derive a factor model, particularly gene factors in this case.

Chairman Binns asked the scientific Committee members if they might comment on the significance of Dr. Kerr's research. Dr. Barlow stated it was impressive that Dr. Kerr started off using gene expression profiling using chips from one set of patients, found several genes of interest, and confirmed 83 of these genes in an independent population. It isn't just the methodological differences, but it was an entirely different patient populations. This was really strong evidence that there was a gene expression profile for CFS patients. Now that this information has been collected, one can go back and refine the data to better understand this link. As Dr. Haley stated, one could go back, in a more unbiased fashion, and see what the clinical profiles can tell us about genetic signatures. Dr. Golomb commented that it was important to note that all of the groups had all the symptoms. Dr. Kerr stated that they had been diagnosed based on the CDC case definition. Dr. Golomb stated that she had always been enthusiastic about finding underlying physiological mechanisms to ultimately define subgroups, rather than subgrouping by symptoms.

Dr. Golomb asked the Committee and scientific audience members whether other researchers had considered looking at other tissue types, e.g., muscle, for gene expression, or was the focus generally on blood samples. Dr. Steele commented that research had been done on spinal fluid. Dr. Barlow stated that it was difficult to obtain these other samples, and if blood gave the signature needed, it was best to start there. The next phase was to elaborate more on what can be determined from the genetic distinctions, for example, which differences may relate to predisposing factors and which things may be causative. She noted that there were several new algorithms that could be run on Dr. Kerr's arrays. It would be important to sequence the genes in the CFS and CFS family cohorts. This would help determine if there really was a genetic predisposition. It would be incredibly helpful to the military because it could identify soldiers with this predisposition and help make determinations about deployment.

Chairman Binns asked if Dr. Barlow was suggesting that Dr. Kerr focus on a particular gene, e.g. NTE. Dr. Barlow stated that in her own work with NTE, they found that subtle deficiencies lead to very different phenotypes in animal models. NTE is also known to be affected by pesticides, and important for glial/neuronal interactions. There may be other just as important genes. However, Dr. Barlow stated that the full sequence of NTE should be covered. Dr. Golomb suggested taking subgroups of individuals with an apparent trigger event and see if there are differences in their manifestations and gene expressions. Dr. Kerr noted that many of their CFS patients were not able to identify a trigger event. Dr. Golomb wondered if he could pick the patients for whom there was a strong case for a single apparent trigger event.

Dr. O'Callaghan noted that the Committee had heard a lot about proinflammatory, neuroimmune processes associated with Gulf War illness. This was an exciting new area, but it was too early to comment too much about the glial/neuronal contributions to Gulf War illness. He noted that Dr. Kerr's nf-kappaB findings fit in nicely here.

Dr. Steele stated that she knew that the objectives of Dr. Kerr's work were to characterize the disease and identify markers, but also to identify treatments. She asked Dr. Kerr to share his thoughts about possible treatment studies for his CFS patients. Dr. Kerr stated that six of the gene signatures might suggest known or experimental therapies. There have been treatments with antibodies and anti-cancer drugs. There was a very small trial of Etanercept showing benefit in six patients. They hope to repeat this trial, and are also interested in testing interferon beta. Unfortunately, they have not acquired the funding to do this yet. Dr. Kerr stated that there had been concern that interferon beta could mimic the symptoms of CFS. The reviewers, however, had seemed more receptive to testing Etanercept again. Dr. Golomb asked whether there had been evidence of unfavorable side effects associated with Etanercept. Dr. Kerr stated that individuals may have a higher risk of tuberculosis, but one could switch to another anti-TNF alpha drug.

Chairman Binns asked Dr. Kerr if he would discuss how he manages his research program. Dr. Kerr discussed the specific arrangements and coordination of the six researchers involved in his program. The group was about to start a CFS clinic, but did not have plans to see Gulf War veterans at this time.

Ms. Denise Nichols, an audience member, asked Dr. Kerr if there were any military veterans in his sample. Dr. Kerr stated that this question was not specifically asked, but he was sure that there were none in the cohort. Ms. Nichols noted that many Gulf War veterans "wander" into CFS clinics and don't identify themselves as veterans. She suggested that he double-check whether there were veterans in his cohort or not. Ms. Nichols also asked whether Dr. Kerr's Gulf War veterans study had been funded. Dr. Kerr said they had been awarded 30,000 pounds to repeat their gene expression studies in Gulf War veterans. Chairman Binns asked Dr. Haley if the UTSW program would include gene expression studies. Dr. Haley indicated that it does.

Mr. Hardie asked Dr. Kerr if they were tracking their CFS patients over time, and if so, were they seeing a progression of their disease and/or additional diseases arising. Dr. Kerr stated that the original plan was to follow ten patients for one year, but they will need to look at more than ten in light of the heterogeneity of the gene expression. Mr. Hardie asked if there were any plans to follow these patients for more than one year. Dr. Kerr stated that there were no such plans at this time.

Dr. Roberta White, a Committee member, commented that in all of the work in CFS and disorders with a psychoimmunologic component, she was most concerned about how stress and stressors were discussed. She stated that stress was not well-defined and this issue is very important in Gulf War-related illnesses. As part of the Committee, she plans to keep track of these types of definitions. Dr. Kerr agreed. Dr. Golomb noted that outcomes can be extremely different depending on what the actual "stressor" is.

Chairman Binns stated that he should take this opportunity to officially welcome Dr. White to the Committee. He noted that Dr. White had spoken to the Committee previously, and that the Committee was very familiar with her recent neuroimaging work in Gulf War veterans.

Dr. Steele noted that Dr. William Reeves had spoken to the Committee about CFS genomic studies at the Centers for Disease Control (CDC). Dr. Nancy Klimas had also spoken to the Committee about her planned gene expression studies in CFS and ill Gulf War veterans. Dr. Steele asked Dr. Kerr if he had a sense of how his gene expression profiles would (or would not) correlate with the CDC findings. Dr. Kerr stated that the CDC studies only used microarray data. These studies did not include a real-time PCR component as his study did. The real-time PCR allowed for more specific differentiating of the gene expression. Dr. Steele said that she understood Dr. Kerr to be saying that CDC had "cast a wide net" and it isn't clear what they had "pulled in." Dr. Kerr agreed with this analogy. CDC had used several

different mathematical and statistical approaches with their microarray data, but at the end of the day, their data doesn't tell one which genes were important nor which therapies should be developed.

Dr. Golomb wondered whether it was expected that there would be specific genes that are important, or could there be a wide range of genes that relate to a certain function, e.g., energetic function. She also wondered if there were known instances in which clusters were defined by a microarray, but later became irrelevant when PCR data were analyzed. Dr. Kerr stated that he was not aware of data or studies that looked at this question. Dr. Barlow commented that the issue with PCR and arrays was that both have an intrinsic false-positive, so one can not say one is more "right" than the other. However, if one does both in independent cohorts, one could corroborate findings. Dr. Golomb understood that this made the data much "better." She was just curious about whether there were any examples where such findings were reported, understanding that false-positives are possible. Dr. Barlow stated that they had, when clusters were driven by a handful of genes with very large differences.

Chairman Binns stated that Dr. Kerr's presentation would stimulate Committee discussions for the remainder of the day and long into the future. He noted that it was remarkable what this small group of U.K. researchers had been able to accomplish and that their work had touched on many themes that the Committee has been examining. He noted that ill Gulf War veterans in the audience had identified with the symptom patterns presented by Dr. Kerr. Chairman Binns stated that he was very glad that Dr. Kerr was able to come and share these findings with the Committee.

The meeting recessed for a break at 10:09 a.m.

The meeting resumed at 10:28 a.m.

When the meeting reconvened, Chairman Binns began by noting that this was a time of great significance in the effort to address Gulf War illnesses. Over the past fifteen years, the U.S. government had spent over 300 million dollars researching the health of Gulf War veterans, and the Committee is charged to advise on this research. But he has had to tell the VA Secretary at the end of each year that federal research has not yet contributed to the one goal for Gulf War research that is in the Committee's charter, that is, that the research make a difference to the health of ill Gulf War veterans.

The program that UTSW was undertaking represented a very different approach to this problem. Chairman Binns said that this approach would not have been taken had it not been for the fact that the $300 million spent to date had not produced the desired results. He stated that since the Committee met in Dallas in November 2006, UTSW and VA had entered into a contract. This contract, in effect, made the UTSW program VA's Gulf War illnesses research program. All involved in Gulf War illnesses—ill veterans, Committee members, VA officials—were grateful for UTSW's willingness to take on this assignment. However, this task came with a great deal of responsibility and expectations. UTSW was no longer one of many research groups pursuing individual pieces of this tragic puzzle. It had been given all the pieces and been asked to put them together. UTSW's work was not going to be measured by how many papers are published, but measured against the standard mentioned earlier, i.e., whether this research makes a difference to the health of ill Gulf War veterans. Chairman Binns added that, even if it were not in the Committee's charter, it is the only standard that matters in the eyes of a much more important group, the 175,000 ill Gulf War veterans who have been sick for sixteen years. These veterans' hopes now rest with UTSW researchers.

Assuming the funding is provided as planned, UTSW will receive 75 million dollars over the next five years to study this problem. And at the end of the day, UTSW researchers will go down as the people who solved this problem or those who did not. Chairman Binns stated that Committee members were

there to help UTSW in this mission. The Committee believed in this mission, as well as the UTSW researchers. There was no other group in this country that was more qualified. The justification for giving all of this money and responsibility to one institution was not that UTSW was "good," but rather the benefit that comes from having a comprehensive, coordinated research program versus than the usual random collection of studies produced by research solicitations. Chairman Binns noted that the Committee had just heard about the advantages of what a smaller team could do when assembled in one location. To succeed, UTSW would have to take advantage of this by coordinating operations closely. The Committee has an obligation to offer its ideas to the UTSW researchers and to ask questions. The Committee must subject the UTSW program to the same scrutiny that it has used in reviewing other VA Gulf War research. The Committee wants to do this to help the UTSW program succeed. Chairman Binns hoped that the researchers present would accept the Committee's comments in this spirit.

Gulf War Illness and Chemical Exposure Research Program at University of Texas Southwestern Medical Center, Dallas: Implementation of the Research Recommendations of the VA RAC-GWI

Robert Haley, MD
Professor, University of Texas Southwestern School of Medicine, Dallas, TX

Dr. Haley gave an overview of the development and activities of the UTSW Gulf War illness research program. (See Appendix – Presentation 2.)

During the presentation of the stratification to be used in the national survey sample, Dr. Steele asked how two groups were designated as being in "high risk" or "low risk" zones for sarin exposure. She noted that multiple incidents potentially associated with sarin exposure had been identified and there could be a danger of misclassification that would "water down" the results. Dr. Haley noted that they had assessed different location strata and indicated he could provide an entire session on the details of how the survey had been developed.

During the discussion of exploring mechanistic questions about how various exposures affect cellular processes in mice, Dr. Barlow noted that if something is negative in a particular system it could be negative for reasons specific to mice. Dr. Haley acknowledged this, and added that it could take more than one year to see effects. These are problems that the merit review committee will have to address. Dr. Golomb noted that results could also be negative for a variety of other reasons. Dr. Haley agreed and noted that the merit review committee was composed of National Academy scientists, some of the best "minds" in this area. The first batch of preclinical proposals would be reviewed by the merit review committee in September 2007. So these proposals were still in their formative stage and input was welcomed.

Dr. Barlow observed that these studies provide models, which were great for hypothesis generation. However, Dr. Haley had the opportunity to work with human patients and negative results in the animal studies shouldn't dictate that the research wouldn't be pursued in clinical applications. Dr. Haley stated that the survey and clinical and preclinical projects were separate efforts aimed at figuring out what was happening in humans. At some point, these efforts should be examined to inform each other, but not determine each other.

During the discussion of the case definition(s) used in the National Survey, Dr. Steele commented that she didn't think it would be a surprise or controversial if a new case definition were identified. It is entirely possible that none of the existing case definitions is the "best" one. However, a problem with Objective #1 is that the Seabees are not representative of the Gulf War veteran population as a whole. Dr. Haley agreed with this point. Dr. Steele stated that it was important to optimize the best case definition in a

representative sample. Dr. Haley said that the first step is to see how radically, if at all, the Seabees have changed since the original study. Dr. Golomb stated that she didn't think case definitions would ultimately be based on symptoms alone. They are going to be based on patterns identified with objective markers. Dr. Haley agreed, noting that other diseases, like Legionnaire's disease, Toxic Shock syndrome, AIDS, etc., were initially symptom-based case definitions. However, over time they were based on objective measures and that was what he would like to see happen here.

Chairman Binns thanked Dr. Haley. He noted that there was a full hour reserved for discussion of the plan outlined by Dr. Haley.

The meeting recessed at 12:03 p.m. for lunch

The meeting reconvened at 1:04 p.m.

Neuroimaging Introduction and Overview

Richard W. Briggs, PhD
Department of Radiology, Division of Neuroradiology, Neuroimaging Laboratory
Gulf War Illness and Chemical Agent Exposure Program
University of Texas Southwestern Medical Center, Dallas, TX

Dr. Richard Briggs provided an overview of the proposed neuroimaging components of UTSW's Gulf War illness research program. (See Appendix – Presentation 3.)

Following his presentation, Dr. Briggs introduced Dr. John Hart.

Gulf War Illness Neuroscience Projects Overview

John Hart, Jr., MD
Professor, Brain and Behavioral Sciences and Neurology
University of Texas at Dallas and University of Texas Southwestern School of Medicine

Dr. Hart provided an overview of the neuroscience projects that would be undertaken by the UTSW Gulf War research program. (See Appendix – Presentation 4.) In response to a point made about the need for longitudinal neurocognitive data, Dr. Steele asked Dr. White if she had this type of data for the Fort Devens cohort. Dr. White said she had collected it for some subsets but not the entire cohort. She also had longitudinal data for a DOD cohort that she had assembled to compare treatment-seeking Gulf War era veterans, both deployed and nondeployed. But it didn't consist of the same battery of tests listed by Dr. Hart. Dr. Hart indicated that he would like to speak with Dr. White about this and that they were willing to adapt their approach if necessary.

Dr. Thomas Ferree, PhD, asked Dr. Hart to clarify the relationship between function and deficits in subcortical areas versus cortical areas. Dr. Hart stated that they were able to examine deep areas of the brain. However, the cortical areas of the brain, which are more practical to reach, are a reflection of the deep structures. He had included the thalamus research to show where something might "go out." Part of Dr. Clausson's work is to find individuals with basal ganglia strokes. Dr. Hart has had patients with thalamic strokes. He can do a lesion model, and Dr. Ferree was right that they could use the cortical memory area changes to double-check if there was a memory problem.

Dr. Golomb noted that Gulf War veterans reported increased problems with all of the neurocognitive functions about which they have been surveyed. She wondered if it was appropriate to just look at the brain areas related to the specific problems listed. Dr. Hart stated that some of the neuropsych studies would address these concerns. The neuropsychological core paradigms are being developed as they go along. While these are the ones planned right now, they will be trimmed back. Also, there are multiple different individuals working in other areas. He couldn't address every issue, but had selected these to target first. Dr. Hart stated it was fair to question whether a veteran responded in a particular way because this is what he had been asked, and that there could be a need to examine other brain regions.

Dr. William Meggs, a Committee member, noted that fatigue was a prominent part of this illness. He asked Dr. Hart what was the effect of fatigue on memory and how would this affect his testing. Dr. Hart stated that there were two experiments included in the portfolio to address this issue. Continuous performance test, piloted in fMRI and EEG trials, produces fatigue on a short-term memory test. Electrically, they will see a drop in alpha and gamma changes and they are working to measure this right now. Fatigue also comes in with relation to the attention and executive function testing. Dr. Hart indicated that they were randomizing the testing and scheduling of the tests to address this concern.

Mr. Mike Hood, an audience member and Gulf War veteran, noted that many of the veterans returning now had a certain "look." Dr. Hart stated that those involved in the program had kept in mind how their findings might be applied to veterans of the current conflicts. Dr. Golomb noted that the signature injury among current Iraqi conflict veterans was traumatic brain injury, which had potentially different characteristics. Dr. Hart agreed that there were different characteristics in imaging and also performance-wise. This "look" can be the result of several different things, and he has seen several different "looks." This was how this research had been targeted, i.e., to provide an investigative model.

Dr. O'Callaghan asked if they were looking at chemical interactions of glutamate inhibitors in these studies. Dr. Hart said that he would like to do this research, targeting "sick" glutamate neurons that are partially functional. From a neurotoxic point of view in subcortical areas, can one stabilize these "sick" neurons? This is one of the hypotheses that they have been debating. Dr. O'Callaghan stated that another option was glutamate overload. Dr. Hart agreed, but noted that the data were hard to get.

Discussion followed about maintaining the afternoon schedule of presentations. Dr. Briggs asked the remaining speakers to limit their comments to the highlights. Chairman Binns indicated that audience questions may need to be limited until the discussion period scheduled for later in the afternoon. He asked that if questions were asked that they be brief, be made into a microphone, and that the individual identify themselves.

Dr. Briggs introduced Dr. Michael Motes, a University of Texas at Dallas researcher.

Testing Hypotheses of Changes in Prefrontal Function Related to Gulf War Syndrome

Michael A. Motes, PhD
Postdoctoral Research Fellow, Center for Brain Health, University of Texas at Dallas, TX, and University of Texas Southwestern Medical Center.

Dr. Motes discussed his group's neuroimaging research on age-related cognitive deficits and how it would be applied in their Gulf War research. (See Appendix – Presentation 5.)

Dr. Briggs introduced Dr. Wendy Ringe.

Fronto-Striatal Systems in Depression and Gulf War Illness

Wendy Ringe, PhD
Assistant Professor, Department of Psychiatry
University of Texas Southwestern Medical Center, Dallas, TX

Dr. Ringe discussed research on the involvement of fronto-striatal systems in depression and how this could be used to examine characteristics of depressed mood in Gulf War illness patients in relation to major depressive disorder. (See Appendix – Presentation 6.) She then provided a brief presentation on high resolution fMRI findings related to material-specific memory in the medial temporal lobes. (See Appendix – Presentation 6.) She indicated that these methods could be informative in studying memory deficits in Gulf War veterans.

Dr. Briggs then introduced Dr. James Bartlett.

Conjunction Memory Paradigm: Preliminary Data

James Bartlett, PhD
Professor, Department of Brain and Behavioral Sciences
University of Texas at Dallas, TX

Dr. Bartlett gave an overview of his group's proposed behavioral and fMRI research to capture aspects of brain function that underlie memory problems in Gulf War veterans. The proposed research will compare the three subcategories of Gulf War illness identified by Dr. Haley with healthy controls. (See Appendix – Presentation 7.)

Chairman Binns thanked Dr. Briggs and all of the speakers for their presentations.

The meeting recessed at 3:05 p.m. for a break.

The meeting reconvened at 3:18 p.m.

Dr. Briggs introduced the next presentations, indicating that they would describe subcores of the neuroimaging core technical projects proposed for the UTSW Gulf War program. (See Appendix – Presentation 3.) He noted that the technical work is subservient to the clinical and neuroscience goals of the program. The individual projects were motivated by specific questions brought to this team of researchers. However, because identifiable differences are expected to be complex, it was important to develop the most advanced array of neuroimaging techniques possible. These projects would need to include technical development, testing, and implementation of the techniques.

Dr. Briggs introduced Dr. Thomas Ferree.

EEG Program for Gulf War Research

Thomas Ferree, PhD
Assistant Professor, Department of Radiology
University of Texas Southwestern School of Medicine, Dallas, TX

Dr. Ferree gave an overview of the types of information provided by electroencephalograms (EEGs) and UTSW's proposed use of EEG in combination with functional magnetic resonance imaging (fMRI) for Gulf War illness research. (See Appendix – Presentation 8.)

Dr. Briggs introduced Dr. Sergey Cheskhov.

MR Spectroscopy at 3T

Sergey Cheshkov, PhD
Assistant Professor, Department of Radiology
University of Texas Southwestern School of Medicine, Dallas, TX

Dr. Cheshkov gave an overview of 1.5T magnetic resonance spectroscopy (MRS) findings in ill Gulf War veterans and how UTSW planned to expand this research using 3T capabilities. (See Appendix – Presentation 9.)

Dr. Briggs introduced Dr. Roddy McColl.

DTI Sub-Core: Imaging Protocol and Prelim Data

Roddy McColl, Ph.D
Dept. of Radiology, University of Texas Southwestern School of Medicine, Dallas, TX

Dr. McColl gave an overview of diffusion tensor imaging (DTI), including DTI findings in multiple sclerosis patients, and UTSW plans for using DTI in evaluating Gulf War veterans. (See Appendix – Presentation 10.)

Perfusion and Regional Cerebral Blood Flow (rCBF) Using MRI Arterial Spin Labeling (ASL)

Richard W. Briggs, PhD
Department of Radiology, Division of Neuroradiology, Neuroimaging Laboratory
Gulf War Illness and Chemical Agent Exposure Program
University of Texas Southwestern Medical Center, Dallas, TX

Dr. Briggs provided an overview of magnetic resonance imaging (MRI) arterial spin labeling (ASL) research done at UTSW and plans to combine this technique with single photon emission computed tomography (SPECT) in their Gulf War research. (See Appendix – Presentation 11.)

Chairman Binns thanked Dr. Briggs and the speakers who presented that afternoon.

Committee discussion – Day 1

To begin the discussion of the UTSW program, Chairman Binns asked the Committee to provide general comments or ask general questions they had about the proposed UTSW Gulf War research that had been presented.

Dr. Jack Melling, consultant to the Committee, commented that the aim of this work seemed to be to make a difference. He interpreted "to make a difference" to mean the development of diagnostic tests and treatment regimens. The research program, in his opinion, should be integrated at the earliest possible stage with what is needed to deliver these end products, for example, treatments for ill veterans. He had seen many cases where high quality research failed to achieve timely delivery of what was required to

those who required it. This is something that needs to be avoided in this case. Dr. Melling stated he was giving this message to the Committee, colleagues at VA, and as a reminder, to Dr. Haley and his colleagues at UTSW. Dr. Melling indicated that everyone needs to remember that "it is never too soon to be prepared for success." All of the indications are that the UTSW research will be successful. Collectively, "we" must be prepared to move this forward to get it to where it is needed, that is, to make it available to 175,000 ill Gulf War veterans.

Dr. White stated that she had pages of comments to share with Dr. Haley. Generally, she was impressed with the level of cognitive neuroscience and the imaging program that had been presented. She indicated that she had three major overarching responses to the presentations. Two words that came to mind were "integration" and "translation." While she hadn't seen the overall core, she hoped that there was a translational core in place, that is, that key clinical individuals were already planning for the diagnostic and treatment paradigms that could be applied at the present time. There are some hypotheses concerning treatment applications and some drugs already being used in other kinds of neurological patients. In the types of environmental health centers that she has run, they have a translational core from day one. In one of her centers, they met weekly on these issues.

Dr. White pointed out that another central issue is that the success of all of these elegant studies rests on who comes in for testing. She was worried about focusing on individuals with the previously identified Syndrome 1, 2, and 3. First, the proposed sample of 80 individuals was not large. One strategy may be to decrease the number of tests conducted and increase the number of subjects. However it is done, the selection of subjects and the basis for selection are going to guide what the researchers would be able to find. There are lots of ways to "slice and dice" the data in terms of exposure, clinical syndromes, genetic profiles, etc. However, with only eighty people, they will not be able to "slice it and dice it" very many ways. This issue, in her opinion, was key for a huge part of the program. Finally, she indicated that she hadn't heard anything about the exposure assessment aspect of the program, and would like to hear more about this component. For example, how would exposures be assessed or modeled? How would exposure information be integrated with the other data? This related to causation. However, it may also relate to parceling out some of the comorbid factors and other issues. She thought it was a very exciting program, and looked forward to seeing it unfold.

Dr. Nettleman stated that she would echo Dr. White's comments. She was struck that it would be hard to put a big sample through the comprehensive imaging program at UTSW. If one would put 10,000 veterans through the neuroimaging program, we would know a lot about Gulf War illness. If we put smaller numbers through, we might know something about a small number of people. Dr. Nettleman asked Dr. Haley if the national survey data would be available in a public database, and if he would provide her with a copy of the survey. Dr. Haley indicated that was possible.

Ms. Marguerite Knox, a Committee member, stated that the program was exciting. She asked Dr. Haley how they would select Phase Two (blood sampling) subjects using the national survey data. Dr. Haley said that blood would be collected from all of the special strata—twins, Seabees, Haley and Steele syndrome individuals, etc., as well as random samples of subsyndromic and well individuals. This would provide an estimated 2064 individuals in the total sample. Ms. Knox asked if these samples would be compared with earlier samples. Dr. Haley stated that this was possible because some of the individuals had been in previous studies.

Chairman Binns stated that, from his perspective, it was obvious UTSW had a tremendous neuroimaging capability. He noted that an alumni organization with which he had been involved at one point had selected UTSW for its upcoming meeting on advances in brain research. Chairman Binns asked Dr. Haley about the cost of the neuroimaging component of this program in relation to the entire research

program. Dr. Haley stated that that the neuroimaging component would run about $20 million over two years. Chairman Binns noted that was about two-thirds of the monies that were allotted for the program in those years. He stated that his "gut feel" was that more money was going into this component than there should be. It was obvious that UTSW was going to "nail this nail." There would be no doubt that there was brain damage in Gulf War veterans, along with findings about memory, etc. However, coming back to Dr. Melling's point, how many times do we have to show these veterans have memory problems? It is very interesting to appreciate what is going on in so many ways in the brains of these ill veterans. They would find "17 ways from Sunday" how these veterans were ill and what was abnormal about their brains. However, he found himself comparing it to what might they find if they were to study Dr. Kerr's patient population in the same way.

Chairman Binns related a situation where Dr. Jose Montoya at Stanford had noticed that some of his infectious disease patients had chronic fatigue and noted that they had high viral antibody levels. Just to treat those high viral levels, Dr. Montoya began giving them an antiviral drug. Serendipitously, he began getting reports that the patients' chronic fatigue was markedly better. Chairman Binns guessed that all of these parameters that could have been studied might have found something, but patients would not have improved. He wished that Dr. Haley had somebody out there "dreaming up" these types of trials and therapies that will get to the core of the problem, rather than defining all of the ways to describe the problem.

Dr. Golomb commented that she shared similar reservations. She stated that the original neuroimaging studies were critically important because evidence was needed of objective changes correlated to illness in Gulf War veterans. The original studies were pivotal in producing these findings. Her only hope is that these findings will correlate with UTSW's new findings and be helpful. However, in and of themselves, she didn't see this as taking a step forward for discovering underlying mechanisms or potential treatments. She found the magnitude of this particular effort to be troubling. This was not because she didn't have favorable feelings towards the research. But she was not sure that this was the right approach or major direction for use of the funding.

Dr. Steele stated that she had a sense of unease about the program as well. She echoed that the neuroimaging projects presented were dazzling. However, the underlying goal was to improve the health of ill Gulf War veterans. She had a feeling that a lot of money was being spent to "paint a picture" of the pathology when we really need to explain the nature of the pathology and determine how to address it. She stated that some money should be spent to characterize it, but questioned whether so much of the budget should be devoted to this aspect. Perhaps there was a bridge between the two, but it was not clear to what extent there were clinical applications of much of the research. An effort to identify clinical applications and treatments was of primary importance. Some people might say you can never identify "too much", but this is not a luxury that can be justified, given the sixteen years that have passed for these veterans.

Dr. White agreed. She thought that treatment research should begin now. It is valuable to have some focused studies of the type described because they provide markers for treatment. Some of the neurocognitive changes and specific imaging findings, especially those that relate to function, might provide evidence to support successful treatment. However, her major concern was that treatment applications be considered today. She noted that she was surprised to hear herself saying this because she understood the position of "How do we treat if we don't understand the problem?" However, a lot of effort today needs to be put towards thinking creatively about treatment. Dr. Steele stated that perhaps the focus of the neuroimaging projects could be to identify those most capable of identifying and testing treatment hypotheses.

Dr. Golomb stated that other research programs have administered treatments, exposed animals and looked at mechanisms, and then correlated these findings with neuroimaging findings. These questions examined both animal and human models. The reality is that sometimes the mechanisms associated with symptoms may be treated even when the brain pathology is not. Understanding biological mechanisms can be important beyond what one can find in brain imaging studies. Dr. Golomb indicated that an imaging component to the program was not disputed, but rather the magnitude of its role in the total program.

Dr. Meggs commented that there were several cases where knowing the mechanism elucidated a treatment that someone would never have identified on a treatment "fishing trip." However, if one did find a treatment on a "fishing trip,' it may help elucidate the mechanism. It is hard to say which way to go. Should one use a shotgun approach for treatment or look at mechanisms? Dr. Meggs stated that all of the different imaging modalities would find abnormal results, but there probably would be overlap in the findings. This is true in stroke and Alzheimer's patients. Once the pilot studies are completed, it may become obvious that some or all of the modalities can be "thrown away."

From his experience putting together coordinated research plans in alcoholism, substance abuse, and neuroAIDS, Dr. Bloom stated that until the diagnostic reproducibility of the syndrome was established, we don't have "ground to put our foot on." Until we establish the variety of syndromes within this diagnostic category, we don't have a chance intellectually and logically to define a therapy. Most therapies for brain-related disease have come from wrong hypotheses. We still don't know why antipsychotics or antidepressants work on some people whom they help. Many of the neurocognitive and structural imaging methods discussed that afternoon were helping to define how many types of schizophrenias there were. Knowing the brain structure and genotype of an ill individual helps in finding new ways to approach these illnesses. However, these are illnesses that no one doubts are illnesses. Dr. Haley's program is an immensely positive effort. While it doesn't lead to the treatment of anybody, Dr. Bloom stated he didn't know if there was reason to believe that there were good treatments for this illness. He questioned whether it was worthwhile to look for treatments before establishing the reality of this diagnosis for the people who decide whether a war-related illness is compensable to those who have the problem. We have to establish the reality of the cause and effect, and that this is a real illness. Dr. Bloom stated that he would like to see treatments, but Dr. Haley's program was devised to find leads to move forward. Dr. Bloom didn't think we should digress from this until we get answers to these questions. There aren't a whole lot of drugs in the pipeline to treat this illness. We don't even know what we are treating. And we don't know which ones to treat with what.

Dr. Golomb questioned whether neuroimaging was the right and primary approach. Dr. Bloom commented that it was the only way to look at these veterans' brains while they are alive. Dr. Golomb stated that there were other techniques, e.g., serum markers, muscle biopsies, etc. Dr. Bloom stated that these approaches "didn't hold a candle" unless they provided information within the diagnostic logic that has been set up for this illness.

Chairman Binns asked Dr. Bloom whether an alternative would be to include gene expression, as Dr. Kerr has done in his CFS research. Could this be a source of useful information as opposed to simply relying on neuroimaging? Dr. Bloom stated that a lot of genetic research was being done to determine the phenotypic expression of brain structure, e.g., small hippocampii, small corpus callosum. This body of research is being well-funded by a lot of other sources. In eighteen months, Dr. Haley's group will be able to take advantage of some of these genotypic markers and see which ones may be used for identifying vulnerabilities or consequences of having this illness. Brain imaging and genotyping are the two hottest technologies right now. If one could define who may have been more vulnerable in the theater of operations because they had small hippocampii, the twin studies will show this. The two

structural profiles that were not on the list but could be beneficial were: (1) Oxygen 15 SPECT because it has more precision in time and space; and (2) magnetoencephalography (MEG) because it has both the spatial and temporal resolution and doesn't require electrical impedance matching. There are VA facilities equipped with MEG that could help validate some of the observations of event-related potential (ERPs) techniques and EEGs. Dr. Bloom stated that Dr. Haley had developed a very good program with a two-year timeline to decide which of these many possible leads was "the lead." Not to devote every effort to getting quantitative analyses of defined brain regions would be to possibly miss a neurological factor of importance.

Dr. Meggs commented that there were preliminary MRI data showing abnormalities that have been reproduced by another research center. This indicates that brain imaging is an important way to go. However, there may be other ways too.

Dr. O'Callaghan shared his perspective as a member of the UTSW merit review committee. He stated that there was an integration of the preclinical study designs that support and integrate with the neuroimaging research. There also was integration among the investigators on the preclinical side, providing a core animal dosing regimen. His concern was with the funding mechanisms that had been established. He stated that it was difficult to define the tasks for each subcomponent of an individual preclinical project. But the different projects had to move forward together to tie into the core that supported the preclinical program, and related to the neuroimaging projects. This needed to move forward to take advantage of the setup in place.

Dr. Barlow stated that she thought both Dr. Bloom and Dr. White were correct in their positions. It is a difficult challenge to do integration and translation when you haven't worked out the disease syndrome. However, she wondered if some component of the neuroimaging program could be more integrated with the clinical objectives. For example, if there were an experimental therapy used in conjunction with neuroimaging, one could see if there was a change in the imaging marker. Problems will arise if a biomarker is identified that doesn't change as the disease is treated. This will take you back to square one. She did not see any project in the proposed program that considered whether identified markers would be changeable and if so, if they changed as systems get better or worse.

Dr. Barlow also raised the issue of integration overall with this huge imaging component. She wondered if the logic for the program's neuroimaging component was "we want to look at prefrontal cortex and the best modality to do this is modality X. So this is why we use modality X." Or was the logic "we have some researchers that are interested in prefrontal cortex who use modality X by chance, so we are going to go ahead and use it." This neuroimaging program might be given more focus. It might decrease costs that the program can take a broad approach using researchers to which UTSW has access. But if the modality available is not the best for the region of interest, such as the hippocampus, should they divert their resources to look at the prefrontal cortex or should they be looking at the hippocampus?

Mr. Steve Smithson, a Committee member, indicated that the discussion had moved away from general comments, so he would forward his comments to Dr. Haley separately.

Chairman Binns commented that he didn't understand a contract where one gets paid after one has already spent the money. Dr. Goldberg, the Committee's designated federal officer, indicated that he couldn't speak to this point. This was purely a VA contracting issue, which is a process outside of VA's Office of Research and Development (ORD). ORD is not consulted or allowed input into the process. Chairman Binns asked Dr. Haley if he could explain the process. Dr. Haley stated that VA Central Office and UTSW were all "on the same page" and that this was not an adversarial process. When this Congressional allocation was first announced, the Inspector General took a strong position that this be

treated as a grant. The problem was VA does not have granting authority, so the only mechanism available was a contract. The Indefinite Delivery / Indefinite Quantity (IDIQ) contract mechanism was actually the best type for this purpose, and other agencies were also using it for the same purpose. The payment in arrears was something of a problem, and they would be discussing this aspect with VA soon. There have been a series of meetings to work through these hurdles, and the hurdles have been overcome. Dr. Haley was confident that future hurdles would be overcome as well. He also thought there would be a finite number of hurdles and that they would get to point where all of them would be solved.

In response to the question "What is a task order?" Dr. Haley commented that it was an evolving art. The National Survey was one task order. The blood bank was another task order. The paraoxonase lab was another task order. The neuroimaging program consisted of 25 task orders. Every box on the program diagram that he presented was a task order. The clinical science task order addressed bringing patients in for clinical tests. Every modality that probed patients was another task order. Every one of these task orders had deliverables and would follow a standard format. Once the neuroimaging core had been written as task order, the following task orders would use it as a "cookie cutter." It may seem wild and crazy, but it was actually logical and, as in a complex grant, provided a different account number for each project. At the end of the process, they will know exactly how much was spent on each project. While it has been "painful" just conceiving and preparing the task orders, it now seemed logical and would allow the program management core to monitor each project "deliverable." From a management point of view, it was doable.

Chairman Binns asked if Dr. Haley thought changes to task orders would be manageable. Dr. Haley thought that they would be. They would have to sit down and design the change carefully, describe it in the contracting format, and then go to the contracting officer with the details. It will then go through the contracting officer's technical representative, or "coder", who will determine whether the change is reasonable or not. If it is, it will be integrated into the wording of the task order. Chairman Binns hoped that the "coder" would develop enough expertise of his or her own to be able to understand why the proposals are being made and will be able to make decisions based upon the logic of the research. Dr. Haley stated that the "coder" on the contract was doing a terrific job. He noted that the memorandum of understanding and IDIQ contract provides that the merit review committee has the final say on science. So the "coder" doesn't review the science. He is reviewing it from a contracting perspective. Are the proposed task orders and/or change in line with what the merit review committee approved? He doesn't review the science per se. However, he is always present and very knowledgeable and objective. He is catching things that the Inspector General may identify objections to later. He has a lot of contracting experience, which is saving them from future headaches.

Chairman Binns suggested and encouraged Committee members to send their comments to the Committee office, who would organize them and send them together to Dr. Haley. This would provide a record for the Committee. Also, Dr. Haley would receive them as a package, but recognize that these were not Committee recommendations but individual comments. He asked if any Committee members objected or had a better idea about coordinating this.

Mr. Hardie thanked the scientists on behalf of ill Gulf War veterans. This was obviously a vast project that involved individuals from a wide spectrum of specialties. From the concerns that he had heard expressed by the scientists on the Committee, it seemed that the resounding one was how to pare back how much was being spent or how to spend money this way versus that way. Mr. Hardie found it to be of political concern and deep disappointment that this program was the "only show going." If there was more money and it was possible to do more of what was happening at UTSW at other centers, he wondered if the same concerns would be raised. He was pleased that the U.S. Senate was considering an amendment to the Military Construction Act that would appropriate funding for the U.S. Department of

Defense's Congressional-Directed Medical Research Program (CDMRP) for Gulf War research into treatments. If this was successful, there would be at least one annual appropriation again that might be able to provide some of the needed treatment research. For the record, Mr. Hardie stated that it was a big disappointment that about $20 was being spent per Gulf War veteran today. It was extremely disappointing that sixteen years after the war this is the small pittance appropriated to Gulf War veterans. It was also a disappointment that so much of the funding in previous years was squandered and wasted on stress research or on things that were irrelevant in order to demonstrate that there was nothing wrong with these veterans. It is difficult sixteen years later to be receiving phone calls from ill Gulf War veterans. Mr. Hardie shared that he had just received a phone call that week from a widow of a Gulf War veteran who committed suicide because he was so ill. He didn't know what to tell these veterans or their families. So he sits on this Committee as an ill Gulf War veteran himself. He indicated that he was pleased with the efforts of those in the room but shared his disappointment that this was all that he and other Gulf veterans have.

Dr. Haley indicated that all of the comments and concerns raised around the Committee table about the direction of the program had been raised and discussed by the UTSW group, that is how to spend this money in a way to get us to a diagnostic test, understanding of the physiology, and a treatment. These are the goals. The question is how to use the money, which is an embarrassing amount of money for which he didn't ask, to achieve them. The governing point of all of this research and the approach they have taken is his belief that we don't know what "this" is. Dr. Haley stated that he did not value very strongly any of the previous studies with positive findings, including his own. He didn't think it was a very convincing amount of literature. We don't really have a good idea of what this thing is, and to overestimate or overinterpret that literature would be to squander a huge opportunity. He added that UTSW's MRI spectroscopy study was performed on 26 ill veterans who had Haley Syndromes 1, 2, and 3, from a group of 250 Seabees. He noted that only 40% of the battalion had participated, too, and that the study has been criticized. He said he was not reacting to critics, but the critics are right that this was not "truth." These are tantalizing clues and nothing more.

Dr. Haley said that the real decision point is whether to forget pathophysiology and understanding what is going on in the brain and go right to treatments, or to try to understand the pathophysiology and not go for treatments. Use of the serendipitous approach to find a treatment? If you are lucky, you will win and win quickly and cheaply. But if you aren't lucky, you will never win at all. Dr. Haley stated that DOD and VA tried this approach ten years ago with a doxycycline treatment study and a cognitive therapy and exercise combination study. These studies were negative and cost $25 million. This was the serendipitous approach. The alternative was the rational approach, which meant they would go in and understand the disease first. Forget treatment for the moment. Once the disease is understood, work could be done designing treatments. Dr. Haley stated that this was a "surer" approach, but it is more expensive and will take longer to do. He indicated that the best thing to do would be to take both approaches with lots of money available to do so. Dr. Haley was confident that UTSW had designed the studies that would get the answers. However every time we cut back, we potentially exclude the "right" answer. He acknowledged that there may be additional things that they could do to broaden the likelihood of finding the right answer.

Dr. Haley added that they were doing a few things that might help them with the serendipitous approach. They have included questions in the national survey to find out if Gulf War veterans were getting better and if so, what treatments were working. If something is revealed, they will then program some money to do a clinical trial. However, he thought it would be a waste of money to go to treatments right now. We don't know anything about this disease. We need to define what the disease is, as well as what its variants and subtypes are. At that point, they can define homogeneous groups on which clinical trials can be conducted. Dr. Haley stated that if he did have a treatment right now, he would have to have a clinical

trial of 10,000 people because of the variety of illnesses. There is so much heterogeneity that a successful drug will have a tiny treatment effect. He noted that it had been sixteen years since the war and thirteen years since research was seriously begun. Ten years ago, people were impatient. We spent $300 million dollars and we didn't get anywhere. We are impatient now too. But if we come up with a really great answer three or five years from now, people will find the value in this approach. Dr. Haley stated that the rational approach will get us somewhere for sure. If signals arise from the survey results, they may be able to start designing a clinical trial. To maximize the probability at this point, we need to concentrate our money on the things that might get us there and then, as quickly as possible, narrow it down to the things that will get us there. Dr. Haley stated that UTSW needed to put the first year's research money into the broadest projects and preclinical studies. He noted that Dr. Gilman and the merit review committee were wise to make these one-year studies, providing direction for the next year's research. Concentrate the monies up front, create the opportunities, and then focus down in a year or two to clinical trials. This was a judgment call, and this was where UTSW had come down.

Dr. Golomb stated that she didn't disagree about the treatment issue. However, this wasn't just an issue of whether to go for treatments or neuroimaging. The brain is obviously an end organ that is affected. However, there may be mechanisms that might be identifiable through other processes for which the brain is an end organ besides neuroimaging. Dr. Haley stated that he understood Dr. Golomb to be suggesting there may be additional options to include in the clinical core, which he was open to doing. These are things that could be done for a minimal cost. The cost is selecting and bringing the patients in for clinical testing. He indicated that he was in the process of trying to find someone who would test for mycoplasma fermentans in this sample. They want this to be the best biomarker study possible, testing as many hypotheses as possible. If there were suggestions to include in the clinical tests, these would be very helpful.

Chairman Binns thanked Dr. Haley. Dr. Haley stated that he really appreciated the input provided by the Committee. Every time these issues are discussed, they get a different perspective and it will influence what they are doing. He indicated his desire to keep talking about these issues.

Chairman Binns noted that there were several members of the public, many who were ill Gulf War veterans themselves, who wished to speak on the record. He asked these individuals to keep their comments to five minutes or less.

Public Comment – Day 1

Mr. Mike Hood, a Gulf War veteran from Wichita Falls, Texas, spoke to the Committee. He wished to discuss the health problems of veterans who served in the Gulf either prior to or after the 1991 Gulf War, but not during the Gulf War itself. He served two tours in the Gulf, one prior to the Gulf War (1988) and one following the Gulf War (1993). He stated that these veterans are not discussed or considered when it comes to health problems associated with exposures in the Gulf. He discussed his own health problems. While some Gulf War veterans look healthy, he asked whether those present would want a blood transfusion from a Gulf War veteran. He indicated that most would not. He stated that everyone who has served in the Gulf since 1982 should be barred from donating blood.

Mr. Ed Butler, national secretary of Veterans of Modern Warfare, spoke to the Committee. He stated that most of the presentations given that day were very relevant to the multiple sclerosis (MS) and MS-like problems facing many Gulf War veterans. Further, he noted that Veterans for Modern Warfare and the National MS Society were working together to see Congress appropriate $15 million to the CDMRP for MS research. He asked the Committee if it would support this effort. He commented that, from his

personal observation, it appeared that the MS and MS-like clusters among veterans throughout the country had occurred in veterans who had been exposed to petroleum products while in the Gulf. This included, for example, oil refineries and manufacturing facilities that use petroleum in their products. He noted that Dr. Luanne Metz, a professor at the University of Calgary, was evaluating the number of MS cases found around the coal mining generators in that region. He indicated that she might be a resource for the Committee. He indicated that there were about 5,000 Gulf veterans who had been diagnosed with MS or MS-like symptoms, but noted that it is unknown how many were misdiagnosed. He understood that the Committee was not focused on MS, but wondered if it would support this type of research.

Mr. Kirt Love, a Gulf War veteran, spoke to the Committee. He stated that while some individuals feel it is a "dead end" and didn't need to be discussed, he believed that the Committee needed to consider whether ammonium percholate exposure during the Gulf War might contribute to the ill health of Gulf War veterans. He stated that Gulf War veterans were exposed during the ground war to a variety of aerosolized agents and propellants. This exposure was specific to combat deployment versus other deployments to the same region. He stated that soldiers were not warned during the Gulf War that they should not be near the vapor trails of the rocket launchers being used or to protect themselves from this particular exposure. The military is aware that this exposure may be harmful and is studying the effects of this exposure now. Mr. Love noted that ammonium perchlorate was now present in the U.S. water supply. Everyone in the room was probably positive for this type of exposure. He stated that this chemical had properties similar to sarin and other types of agents in theater. It was also testable via urine analysis or other methods. Mr. Love said that no studies of aerosolized ammonium percholate had been conducted, even though the government was aware that there were lethal concentrations on weapons ranges around the country. Most of the studies conducted have examined the water supply. This exposure is being trivialized even though there is little data on it.

Mr. Love expressed his displeasure that there were no Gulf War clinics, programs, environmental coordinator, or kiosk at his VA facility in Temple, Texas. He stated that this facility had more Gulf War veterans than any other VA facility in the country. He has brought this issue to the attention of VA Public Affairs, all the way to the senior coordinator at VA's Central Office in Washington, DC. Mr. Love stated that he was part of the effort that put in place the laws for these programs and was disappointed that VA had not been able to properly diagnose his condition. He is now seeking treatment, but it may be too late. He stated that short-term, not long-term, programs needed to be pursued, because veterans like him have no place to go right now. He stated that it had been announced that there would be a clinic with the UTSW program. However, VA has managed to turn it into something else. Every time veterans almost have a place to go for help, they are robbed of it. He said that the only reason he was alive was that he was conducting his own dietary trials and living in extreme measures. Medications didn't work for him and actually resulted in adverse reactions. The best he can do now is to do the dietary trials, e.g., dark chocolate. He has had to do these trials himself because there was no program or place for him to go for help. He indicated that this was not the fault of the Committee, but asked that it consider recommending small, short-term solutions, which could be done in conjunction with brain imaging. He stated that research was needed on real-time imaging, as well as long-term functional imaging. There were a variety of ways to do both short- and long-term research. A two-fold plan was needed.

Ms. Becky Cann, a Gulf War era veteran, spoke to the Committee. Ms. Cann did not actually deploy to theater because she became ill from the vaccines administered in preparation for deployment. She stated that she was sicker than many of the troops who were deployed. She received her vaccines in November 1990 and became ill almost immediately. She tried to deploy for several weeks, but was finally told that she would never be able to and would not recover. She said that she had found a treatment, thanks to an anti-aging physician. It involved IV therapy and sub-lingual medications, most of which are hormones. Oral medications did not work. She stated that she had been exposed to uranium too. If you lived in a

mining town or served in the Gulf, you were going to get sick. She stated that there were nine uranium mines in South Texas and the Rio Grande area. She has been forced into retirement, but is not eligible for Social Security. She stated that she had the same infections, chronic fatigue and cognitive function problems that affect deployed Gulf veterans. Their brains have changed. There are days that she can not drive, prepare her meals or even shower. She has had to seek this treatment on her own. The VA has diagnosed her as a "psych case." Anti-depressants cause people to commit suicide and go into rages. Their adrenal glands don't fit the description of people who are depressed. There is a need for tests, like brain scans, to show that there is a cascade of physiological events that have changed these veterans' DNA, hormonal system, adrenal glands, and brains. Veterans need treatments today because they were looking down the barrel of death.

Ms. Lauren Billings, a Gulf War veteran who was a navigator on an Air Force KC-135 air refueler, spoke to the Committee. She stated that to be on an air crew, you have to be one of the healthiest of the healthy. She served in the military from 1989 to 1996. Before she was deployed to the Gulf, she would become sick from her vaccines, which was dismissed by the medic. When she returned from the Gulf, she began experiencing extreme fatigue. She asked the physician if she had mononucleosis, chronic fatigue syndrome, etc. She began researching thyroid and immune issues. In the fall of 1998, she developed vision problems, which included sensitivity to light. After having a MRI and spinal tap, she was confirmed to have MS. She indicated that she was part of a minority among Gulf veterans, having received an actual MS diagnosis. She is trying to hold down a job which can be difficult because of the fatigue and cognitive problems. This has been particularly difficult because she has received a graduate degree, but no longer can remember and learn things like she used to. She also has two young sons that she is not able to interact with like she would like. She is sensitive to extreme heat and cold and can't be outside with them much. She does take Copaxone, but this is only slowing down the process. She recently found out that she has a family history of severe reactions to vaccines. Because she has been sensitive to all of her vaccines, she has not vaccinated her children. She expressed reservations about taking a good immune system and "revving" it up with "stuff," including metals.

Ms. Denise Nichols, a Gulf War veteran, spoke to the Committee. She noted that the Committee had reviewed oxidative stress, mitochondrial damage, and a broad range of other topics at its last several meetings. She was thrilled to see this progression. She wanted to keep pushing for all specialties and concerns to be included in the discussions. There should not be a single focus on neurological concerns. She stated that there appeared to be some bias against anti-aging and environmental doctors. She wanted the Committee to create a round table approach and invite all these parties and specialties to join in the discussions. She noted that there were at least three anti-aging and environmental physicians in Dallas, but none were invited to speak to the Committee. She indicated that they have treated Gulf War veterans and should be allowed to speak to the group. Ms. Nichols indicated that she loved Chairman Binns' charge to UTSW, as well as Dr. Kerr's presentation. Despite all of the ups and downs, she had a lot of hope. She asked that handouts of the meeting presentations be provided to the audience so that it would be easier for them to follow along. She indicated that it was difficult for the veterans to multi-task now. She also noted that there were social / interpersonal relationship problems among Gulf War veterans. Many were working to compensate, but were also dealing with fatigue and neurocognitive problems, which lead to these problems. She asked Dr. Haley if there were measures for these social and behavioral problems. She stated that they were not like this before the war, and they were fighting not to be so now. It has led to problems with their families. She also noted that Gulf veterans became tired faster, had noise sensitivity problems, and sexual dysfunction for both male and female veterans. She noted that she had a few suggestions that she would like to make for the UTSW program. There was a lot of money and it needs to be used in manner that "works." Testing for pituitary function and thyroid hormones should be done on all the individuals brought in for the clinical phase of the study. There are things that we can do to help these veterans.

Chairman Binns thanked the veterans who spoke.

The meeting recessed at 5:48 p.m. for the day.

Day 2

The meeting reconvened on Thursday, July 19, 2007, at 8:33 a.m. at the Hilton Anatole, 2201 Stemmons Freeway, Dallas, Texas. Dr. Nettleman was not present for the second day of the meeting.

MRI Reveals Evidence of Structural Brain Differences Among Veterans Deployed to the first Gulf War

Roberta White, PhD
Chair, Department of Environmental Health
Boston University School of Public Health

Dr. White gave an overview of her research team's preliminary findings on structural brain differences that distinguished Gulf War veterans with high levels of symptoms from those who were less symptomatic. (See Appendix – Presentation 12.) These findings had previously been presented at a scientific meeting, and had been reported in the press. Analyses were not yet complete, but Dr. White indicated that she was confident about the findings because they had also found a relationship with function.

Ms. Knox asked Dr. White if she thought her findings indicated brain atrophy in these Gulf War veterans. Dr. White said that it was unclear. It could be brain atrophy but it could be their brains were always smaller. She commented that the press releases about the study suggesting a "shrinking" of the brain, but she was not sure this was the case. She added that the issue of causation would be clearer when she was able to look at the exposure-related outcomes. If she found clear relationships between brain measures and exposure to sarin and cyclosarin or pesticides, she would be more comfortable saying the brain change was related to some causative factor. However, it could have been a risk factor. That is, individuals who have smaller total cortical brain areas might have been more susceptible. This would be incredibly important to know because it would tell us who to worry about and who might be particularly vulnerable to an experience like the Gulf War theater. She was not able at this point, however, to say if the differences were due to shrinkage or a pre-existing structural difference. Ms. Knox asked if any of these veterans had had MRIs prior to serving in the Gulf War. Dr. White stated that none had, but they did have scans from one or two from the 1990s. She has been advocating that predeployment testing include imaging, but to her knowledge this is not happening.

Dr. Meggs asked if the study participants had been asked to donate their brains to medical science upon their deaths. Dr. White stated that they had considered asking for several types of tissues to bank. They had made a big effort to bank blood, but VA would not allow it. If they had the bloods from these veterans, they could look for new genetic information and perhaps biomarkers. Brain banking is a good idea, but it was far beyond what she was funded to do. She indicated that one study participant had called her recently asking how to donate their body to the medical school.

Dr. Golomb noted a recent study looking at magnetic resonance imaging in patients who had self-reported cognitive loss and found that these patients had, on average, greater brain atrophy than control patients, despite having normal neuropsychological test scores. This is another reason to listen to one's patients

when they have something for which you have not yet identified a measure. Dr. White agreed and characterized her findings as preclinical. Since the New York Times article came out, she had spoken with many Gulf veterans who had white matter lesions. But she didn't think it was just matter of brain lesions, but the small differences in volume. It was similar to the situation with neuropsychological test measures differences that are often not considered clinically significant. For example, one would not diagnose amnesia from the differences identified in the California Verbal Learning Test. What subclinical and preclinical findings tell us is that it is important to listen to patients' complaints when they don't meet diagnostic criteria for something. Exposure to chemicals and other things can result in symptoms and changes in brain function that aren't "big" enough for us to see clinically.

Dr. Golomb noted that the normal range for these cognitive tests encompass a wide range of people and levels of ability. A person can have marked cognitive losses that affect their daily lives and job performance and still fall in the normal range. Sensitive pretesting, followed by post-testing, was needed to determine the variation, but this was difficult to establish in an individual. Dr. White commented that this was not case with neuropsychological testing, since the baseline was not set at "average," if average is what you call "normal." The baseline used a model of what people were like before a brain insult. Many CEOs get early MS and no longer can be a CEO. They may obtain a normal test score, but it is still a standard deviation or two from their baseline.

Dr. Barlow asked if other brain areas were examined, and if so was this area the only one in which abnormalities were found. Dr. White stated that that they examined about 15 brain areas and total volumes during the preliminary analyses. These were the targeted areas. They are now looking at everything, as well as all the white matter measures.

Dr. Haley stated that this was an important question for anybody doing neuroimaging studies. He frequently gets calls from veterans who have had a brain scan, asking for his thoughts on the results. Many times the lesions seen in the white matter are probably the unidentified bright objects (UBOs) that neuroradiologists see. In his previous studies, SPECT scans and MRIs were conducted on cases and controls. They found that the UBOs were the same in the sick and well subjects. This is true in neuroradiology in general. These UBOs are bright specks that appear to be defects in the white matter. However, they are really nonspecific findings and may have no clinical significance. This is controversial. Some people may say they do have significance. But he believed that they don't appear to be related to disease and symptoms. He added that his group had conducted SPECT scans because of the growing research using this technique on people with unidentified illness. They had done a study where three or four radiologists read the scans of cases and controls blinded. They found that there was not one lesion that more than one radiologist identified, and these findings were the same in the cases and controls. Quantitative comparisons were needed. And there also needs to be a very good control group or good series of "normals" to which one is comparing values, e.g., volumes, lesions, etc. He thought that things that radiologists see visually are not related to this class of illness.

Dr. White questioned this, and noted that there was a way to take digitized measurements of white matter lesions. There also was a lot of evidence that having more white matter lesions was associated with mild cognitive impairment. There are also studies showing dose effect relationships between the amount of white matter and cognitive change. She agreed that it was controversial. If you talked to a clinical radiologist or neurologist versus a neuropsychologist or a vascular dementia expert, you would get differing opinions. Dr. Haley thought that they agreed. If one digitized lesions or volumes and compared them to normal values, this was reasonable and should be done. But they shouldn't rely on a visual interpretation of a neuroimaging scan, which are the main source of questions from veterans. Dr. White agreed, but noted that they can do these automated readings without doing a special kind of scan. There are two reasons she started using neuroimaging in the 1990s. First, brain scans deliver a strong public

health message. When she conducted neuropsychological testing, she might believe there was an exposure/outcome relationship and changes in the brain of the patient. But she knew that these findings did not have the same impact as pictures showing a brain difference related to sarin exposure. The other reason is that post-processing techniques are improving every day. They can take old scans and do new processing and find amazing things.

Chairman Binns stated that he had found Dr. White's studies very persuasive because they were imaging studies. One didn't have to go through an extra layer of interpretation, which may be easy for well-informed scientists to understand, but was less obvious to lay people. Similarly, he understood neuroimaging better than the functional tests, e.g., moving pegs around on a board. He asked Dr. Haley if straightforward volumetric imaging that could be matched with comparable psych tests was included in the proposed research at UTSW. Dr. Haley indicated that it was.

Dr. Steele commended Dr. White for her research approach, and specifically for the parallel studies that correlated imaging findings with studies of function. She also pointed out that Dr. White had symptom data on this cohort at repeated intervals since just after the Gulf War. On the question of whether individuals with smaller brain volumes had been more susceptible to exposures, she wondered whether this was testable in animals. Dr. White stated that it could be tested depending on the animal model. She wasn't sure whether mouse models would be sufficient. She is using a primate model looking at the effect of mercury on white matter. This provides a better comparison of brain changes but it is very expensive.

Dr. Bloom commented that there were a lot of data on mouse models of human neurodegenerative diseases. One could do high resolution tests, e.g., 9 Tesla MRI, that bring the resolution down to 100 microns volumetrically. A transgenic mouse line has been established for Alzheimer's disease. Changes can be seen in a matter of 4-5 weeks. Generally, the problem is not tissue degeneration but rather failure to proliferate and achieve adult status. These mice start out with smaller hippocampi, for example. This suggests that the genes that cause human neurodegenerative disease may strike a lot earlier than the pathological findings that are observed when symptoms present. So these animals enter an exposure period with a smaller than normal brain. Similar studies have been done on mouse models of ALS. One can spot, with high resolution, early changes that precede the motor weakness that occurs. However, he was not sure there had been a study done across mice strains with sarin exposure for long-term chronic effects. It is would not be a cheap study to do. He had a contract with CalTech, who had a 9.4 Tesla machine, to do a similar study. It cost him about $5,000 per mouse. However, it was an approach that didn't require the removal or dissection of the brain. It allowed him to see gray matter and white matter boundaries and could segment and show findings for selected brain regions. The key was to have good hypotheses before conducting this type of study. Dr. Steele expressed surprise that it cost so much to study animals. Dr. Bloom noted that these animals were dead and could be scanned over nine hours. A human could never lie still enough for that period of time. Also, the heartbeat and respiratory rate of a mouse are such that one loses resolution if the animal is alive during the scan. It "jiggles" the brain and causes the boundaries between grey and white matter to be blurred. Because these animals are clones of each other, one doesn't have to follow an individual animal. The next generation will be exactly the same.

Dr. Barlow commented that we don't know if these structural differences in Gulf veterans predisposed them to developing the symptoms or were the cause of it. When one tries to model this in an animal, one has to figure out how to create a model that is predisposed. We don't know what this would be so you would need to begin with a range of animals with different brain types. But since we don't know what causes differences in brain types, you might not pick the right reasons for the brain types. Until we better

understand the genetics that give rise to differences in brain size, it would be very difficult to study this in an animal model.

Dr. Golomb commented that to assume that the smaller brain volume predisposed one to the injury, one would also have to posit that individuals with smaller brain volumes were also selectively exposed to more sarin. Dr. Barlow stated that one would have an increased risk for damage from the same level of exposure. Dr. Golomb understood this, but thought Dr. White had also found that people with higher quantitative exposures had more brain atrophy. Dr. White said that they had found a dose-effect relationship in the white matter volumetric findings. She believed this provided support for suggesting that sarin might be a causative factor for the brain volume differences.

Dr. Steele asked if there was any literature on what it means clinically to have reduced brain volume in the areas described by Dr. White. For example, does reduced cortical volume correlate with a specific condition or problems? Dr. White stated that there was quite a bit of literature on the relationship between structure and function. This was part of the neurocognitive field discussed during the previous day. There is considerable literature on individual diseases as well. Dr. Steele asked what other diseases or conditions might be associated with findings similar to the reduced brain areas identified by Dr. White. Dr. White indicated that one disease would be MS. She thought MS was an interesting example because there were a number of neurotoxicant exposures that have been related to the development of MS. Another example might be some forms of epilepsy.

Ms. Knox asked Dr. White if any of the veterans in her study had been diagnosed with MS or if MS had been ruled out as a cause for their symptoms. If they had atrophy and lesions, did any have optic neuritis or spinal fluid testing? Dr. White replied that the patients she had described did not have, by definition, lesions. One study participant did have MS and lesions but his data were not part of the analyses that she had presented. Ms. Knox asked how they had differentiated the lesions from the UBOs. Dr. White indicated that they had quantified them and that she didn't have all of these data yet. There was a total white matter lesion volume measure. But none of the patients from the data shown that day had clinically abnormal scans. Two independent radiologists found the scans to be normal. They did this in order to inform participants about whether or not they had abnormal scans. These individuals did not have lesions, but rather had differences in specific structural areas. This is what she meant by examining the subclinical or preclinical picture.

Dr. O'Callaghan stated that he had been impressed with their finding of a decrease in the cortical volume. If this was viewed as an atrophy that had started at a certain point, this was a larger decrease than he had ever seen with other neurotoxicant exposures, including a host of demyelinating agents. He asked if there was age-related loss of myelin volume that could be detected with MRI. Dr. White said that there was and that they had adjusted for this. Dr. O'Callaghan asked if there was a gender difference. Dr. White stated that some researchers thought there was, but others didn't so they had been looking at it both ways.

Chairman Binns opened the floor to the public for brief questions on the presentation.

Mr. Hood asked if Dr. White had been able to distinguish the veterans based on the areas to which they were deployed in the Gulf War. Dr. White stated that they had self-reported veteran location data, unit information, and some GIS-coded data related to where the veterans were at various times during the war. Mr. Hood asked if Dr. White was aware that there were other areas besides Khamisiyah that were sites of possible chemical and biological exposures, for example, Al Nasiriyah and Tallil Air Base.

Ms. Nichols noted that neurocognitive testing was an element of the Gulf War registry exams. She asked Dr. White if any of her study participants had had one of these exams and if so, would she be able to

repeat this testing and would it be an effective measure. She also wondered if a veteran had a predeployment IQ measurement, whether (1) new IQ measures should be obtained, and (2) would those measures have been adequate. Dr. White said that she avoided using IQ measures, except as a sort of control measure. She indicated that they did have previous neuropsychological data for many of these participants from previous study visits. The point of doing the California Verbal Learning Test and peg board was to look at function. These two tests showed consistent effects that were related to self-reported and other exposure measures.

Chairman Binns thanked Dr. White.

Chairman Binns introduced Dr. Bill Meggs, a Committee member and Chief of Toxicology at East Carolina University School of Medicine.

Environmental Medicine and Gulf War Illnesses: Does the map fit the territory?

William J. Meggs, MD, PhD
Chief, Division of Toxicology
East Carolina School of Medicine, Greenville, NC

Dr. Meggs gave an overview of environmental medicine, including discussion of diagnostic techniques and treatment, and how this area may inform the diagnosis and treatment of ill Gulf War veterans. (See Appendix – Presentation 13.)

Following Dr. Meggs' presentation, Dr. Steele inquired whether the pupilography testing was used for people who were routinely exposed to organophosphates or other pesticides, and also whether it could be informative only near the time of exposure, or even years after exposure. Dr. Meggs stated that the Ishikawa study participants had acute organophosphate poisoning, then recovered and were tested at a later point. It was not acute exposure testing. The occupational studies brought in individuals who were exposed every day to organophosphates, who tolerated the exposure and were still working. Using the control group, they were able to show these exposed workers had abnormalities. Dr. Steele asked if Dr. Rea had used this type of testing in his patients who are long removed from their exposures. Dr. Meggs indicated that Dr. Rhea did use it. He indicated that the testing did not have value for treatment, but did document subtle, subclinical brain damage.

Dr. Steele noted Dr. Meggs' discussion about parallels between sinusitis and rhinitis symptoms and chemical sensitivity. She asked whether successful treatment of the upper airway symptoms had any benefit for other chemical sensitivity symptoms or systemic symptoms. Dr. Meggs said that he had prescribed nasal steroids and antihistamine decongestants for these patients, but many could not tolerate the nasal spray due to irritation. He had found Nasalcort AQ, which is an aqueous solution, to be better tolerated. The really severe patients, the ones who had chronic fatigue, neurocognitive problems, etc., did not seem to be helped by these treatments. From his clinical impressions, individuals who were compliant with creating a clean environment and avoiding chemicals did get better in time and became more tolerant. However, they never lose their chemical sensitivity. He was only aware of two instances where an individual was reported to have been cured. One was reported in a religious book that discussed medical healing. The other case reported a cure resulting from hypnotism. If it is really a neurological pathway set up to cause severe localized reactions to stimuli, which are acquired via learned behavior, this might explain these outcomes. However, his experience was that most people get better over time using avoidance techniques and limiting their chemical exposures, but they were not cured.

Dr. Bloom noted that Gibson's study did find that prayer was the third most effective treatment. Dr. Meggs indicated that was correct.

Dr. Golomb said that her clinical experience with chemical sensitivity patients mirrored Dr. Meggs' experience. She indicated that she had a couple of patients who went to another country and upon return had severe reactions. She stated that there was evidence that in conditions involving oxidizing stressors, the body upregulates antioxidants, but not necessarily at levels sufficient to return to normal. She discussed research at the University of California at San Diego's that looked at sinus irrigation as a treatment. Many of her patients who have used this technique have given up nasal inhalers, which was good considering their chemical intolerance.

Dr. Steele noted that there had been a VA physician, Dr. Myra Shayevitz, who was familiar with multiple chemical sensitivities, and had a clinic for Gulf War veterans in a VA hospital that incorporated environmental controls. Dr. Shayevitz never did a formal study, but reported to Congress that she had treated 25 patients and had some positive results. Several of these patients wrote letters to Congress about the success of their treatment. Dr. Shayevitz believed that this type of study should be done on a larger scale for Gulf War veterans. Dr. Meggs commented that it would be easy to create one of these environmental control units in a VA facility. Because the facilities are typically of older construction, simple modifications and bans on chemicals on the ward would allow for the creation of a reasonably controlled environment. Dr. Steele said that Dr. Shayevitz's unit did not require construction, simply the banning of chemicals and education of patients on how to avoid chemicals. Dr. Meggs stated that this would be easy to do, i.e., creating a relatively clean environment compared to the living environment of the average person.

Mr. Hardie related his own experience with multiple chemical sensitivities, sinusitis, and lung problems. He indicated that he had sinus surgery 10 years ago, involving the removal of bones and mucous membranes. He found that until swelling returned eighteen months later, he had some of the worst sensitivities in his life. He wondered if Dr. Meggs had heard similar complaints from others. Dr. Meggs indicated that he had. A parallel would be the observation that bronchodilators increased mortality from asthma. One reason is that the bronchospasm is being treated but the inflammation is not. Inflammation is what individuals die from. Bronchospasm is actually a protective reflex. It is triggered by sensory C-fibers in the upper airway. When a noxious stimuli enters the airway, a neural reflex creates a bronchospasm to protect the lung and a burning sensation to prompt flight. Dr. Golomb said that another issue was that beta-agonists cause down regulation of beta receptors in the airway. So when one experiences a bad exposure and goes to use his or her inhaler, it is no longer as effective. Dr. Meggs added that asthmatics were more likely to die from mucous plugging and other inflammatory response than bronchospasm. He acknowledged that it was a multifactorial situation. He noted that one of the effects of corticosteroids was to upregulate the beta-receptors so that bronchodilators work. But the point was that bronchospasm was only one component of asthma, which is an environmentally-induced, pathological alteration/inflammation of the airway.

Chairman Binns noted that many members of the audience had experiences related to these conditions and treatments and he would like to hear about them. However, due to time constraints, he could offer them the opportunity to speak at this point of the meeting or at the scheduled public comment period later in the day, but not both.

Mr. Hood spoke about his experiences with multiple chemical sensitivities and other health conditions. He learned on his own over time how to avoid bad environments and exposures. Many Gulf War veterans are self-reporting similar symptoms, but VA has "shut the door" to them. He noted that Gulf

War studies exclude those veterans who served in the Gulf but not during the 1990-1991 war itself. He is working to get Gulf War veterans involved in addressing this issue.

Dr. Ruth McGill, a physician and audience member, spoke to the Committee about her personal experiences in an environmental control unit. She indicated that, in reference to Dr. Haley's and Dr. White's studies, her neuroimaging results had been positive. In her own case, she was able to establish the connection between environmental exposures and her condition. She stated that the nervous system was a two-way street. The nervous system "talks" to all of the other body systems, especially the immune system, and will raise alarms. One of the things that an environmental control unit does is minimize the stimulation and makes it possible to clarify what the actual stimulants are. This provides relief for the patient who enters one of these units. However, when the patient leaves the unit, the suffering starts all over again. Dr. McGill indicated that she created an isolated environment for herself at one point, living in a "ceramic box" in the desert with care by a visiting nurse. She indicated that she had a lot to share about the treatment of multiple chemical sensitivities. She was happy to answer any questions that the Committee might have, providing more details than had been presented by Dr. Meggs. She indicated that she could be contacted through her website.

Chairman Binns thanked Ms. Nichols for suggesting that this topic be discussed at a Committee meeting. She indicated that she would comment later during the scheduled public comment period.

Mr. Hardie noted that many present in the room had tried several of the treatments listed in Dr. Meggs' presentation. He noted that use of alcohol nasal spray on mucous membranes was an experience that would not be soon forgotten.

Chairman Binns thanked Dr. Meggs and said he believed that a lot could be learned from these experiences. If nothing else, it seemed to him that pupilography testing was an inexpensive way to test the autonomic nervous system. Dr. Haley indicated that the method was included in the UTSW research protocol. Chairman Binns was glad to hear this. He noted that it would be difficult for many VA facilities to adopt some of the more exotic and expensive imaging techniques.

The meeting recessed for a break at 10:54 a.m.

The meeting reconvened at 11:08 a.m.

Dr. Ferree gave a brief explanation about a handout he had brought with him to explain UTSW's decision to use EEG, rather than MEG, testing in their Gulf War research program.

Chairman Binns thanked Dr. Ferree.

Update on Research in Persian Gulf War Veterans Illnesses

Beatrice A. Golomb, MD, PhD
Associate Professor, University of California at San Diego

Dr. Golomb gave an overview of published research related to the health of Gulf War veterans that had emerged since the Committee's last update in November 2006. (See Appendix – Presentation 14.)

Chairman Binns thanked Dr. Golomb and asked Dr. Steele to proceed with the discussion about the Committee's report that was being prepared.

2007 RAC Report: Discussion of Recommendations

Lea Steele, PhD
Scientific Director, Research Advisory Committee on Gulf War Veterans' Illnesses

Dr. Steele reviewed the comments and the types of changes and additions that had been recommended by Committee members in relation to the draft report discussed at the Committee's April 2007 meeting. (See Appendix – Presentation 15.) She asked Committee members for their opinions and input on additional types of recommendations that had been raised by members.

Dr. Golomb wondered if it would be useful for the Committee to recommend that veterans avoid exposure to chemicals. Dr. Steele stated that this was implied to some extent by some of the information in the report, but that since these were research recommendations, the focus should be on collection of data. She said that anecdotal reports suggest that chemical avoidance is a good thing. But it would be nice to establish scientifically whether this was helpful to veterans or not. Such findings could also provide a basis to make a formal recommendation for a clinical trial of chemical avoidance. Dr. Golomb indicated that there was evidence to support this type of recommendation.

In the discussion of the need for additional follow-up of the large national epidemiologic study conducted by Dr. Kang, Dr. Melling asked if any gaps had been identified in Dr. Haley's and Dr. Kang's epidemiologic studies. If so, he wondered if the Committee should suggest that work be done to develop a study or studies to cover these gaps. Dr. Steele said that Dr. Haley indicated he had incorporated some of the questions that had not been answered by Dr. Kang's original study into the UTSW National Survey. But if Dr. Kang did a follow-up study again, it would be good for him to address some of these questions. Dr. Steele added that Dr. Kang's initial follow-up study had not originally asked about multisymptom illness or changes in symptoms over time. But he had accommodated a request by the Committee to incorporate this information into his study.

Dr. Haley commented that it was important to think separately about Gulf War illness/multisymptom illness and rare neurological disorders like Parkinson's disease and ALS. This is because no survey will capture these disorders. The VA has a huge clinical database that could be utilized. Dr. Haley noted that Dr. Kang did some preliminary analyses and presented them a few years ago, but they were unsatisfying and incomplete. Dr. Haley suggested that the VA conduct surveillance for these conditions. Dr. Steele noted that this recommendation had been made previously. However, it had been suggested that most veterans who have these conditions are not being treated at VA. Due to the delayed onset of some of these diseases, many veterans do not connect the condition with their service. Dr. Steele added that there would also be a need for a comparison group of nondeployed veterans to determine if there was an increased disease rate in deployed Gulf War veterans. Dr. Haley thought such surveillance could be done for those with ALS using mortality data because of the short period of time between onset and death. So the incidence rate was about the same as the mortality rate. Dr. Haley stated that surveillance of brain cancer should be done as well.

Dr. Haley asked about the status of the ALS registry at Duke University. Dr. Steele noted that this was a passive registry that had identified only 50 cases of ALS among Gulf War veterans, and this number was dwarfed by the large number of registry participants from other eras. Dr. Haley reiterated that he still thought there was a need to conduct surveillance of the VA database for these neurological conditions. Dr. Steele stated that there was a general recommendation to monitor for increased cancer and serious neurological disease rates. The Veterans Health Administration database could be included as an example of a source of information to monitor. Dr. Haley agreed that such a suggestion should be made.

He noted that when one was first considering such a study, he or she could probably think of five different reasons why it shouldn't be done. However, a good epidemiologist can think about the question/problem carefully and can probably figure out a way to make the findings meaningful. It is a surveillance tool. It is not an accurate measurement of incidence. However, through surveillance, one might be able to detect if case numbers appeared to be "passing the threshold." Dr. Haley noted that MS was a fairly common disease with a known age distribution. He thought that creative analyses could be done with the data in the VA's databases to see if the rate of MS was above an accepted threshold. Dr. Steele said that this approach might raise a red flag.

Aside from using this approach for rare diseases, Dr. Steele asked Dr. Haley for his thoughts on reassessing disease rates longitudinally at specified intervals. Dr. Haley agreed that this would be good to do too, noting that consideration had to be given to optimal intervals, funding available, new research discoveries that might inform about new treatments, etc. He suggested 5-10 year intervals with ongoing discussions about when specifically to do it and which data collections should be repeated. Dr. Steele noted that with the data from Dr. Haley's and Dr Kang's samples, along with mortality data collected down the road, they would have self-reported symptom and exposure data on a large sample that could be related to health outcomes and mortality. Dr. Haley agreed.

Dr. Steele asked the other Committee members if a recommendation should be made for additional longitudinal evaluations to follow-up Dr. Kang's original study. The general consensus was "yes." Dr. Meggs stated that it should be done at least every 10 years, but the interval may change if case reports suggest an increase in any particular condition, e.g., MS. Chairman Binns commented that he believed that additional epidemiologic study of neurodegenerative diseases, including MS, had been covered by a recommendation in the Committee's 2004 report. Based on this recommendation, the Senate Veterans' Affairs committee had written a directive into the VA authorization bill for FY2008 that this study be conducted. Other high risk illnesses might also be addressed by this mechanism.

In relation to the discussion of the potential for chemical exposures after the war to have precipitated or exacerbated illness in Gulf War veterans, the Committee indicated its consensus for a recommendation that Gulf War epidemiologic studies collect data on onset and/or exacerbation of Gulf War illness and other conditions in relation to exposure to hazardous substances subsequent to Gulf War service.

Dr. Steele then provided background information on issues that had been raised in relation to the Institute of Medicine's (IOM) Gulf War and Health series of reports. With regard to the update report on sarin exposure that was part of this series, Mr. Smithson noted that the IOM report had not reflected the reason it had been commissioned to reexamine effects of sarin. He noted that the reason for the request was to consider animal study data, but the IOM did not seem to acknowledge this. Chairman Binns stated that the letter from former Secretary Principi was very clear in saying why he was requesting that IOM reconsider the evidence of health effects related to sarin exposure. The disconnect between the report and the reason for the report had happened further downstream in the organization.

Dr. Golomb commented that her father was in the National Academy, and he had commented that National Academy reports are known to be reports "for hire." Often, individuals who are not in the National Academy prepare the reports with conclusions in favor of whoever funded the report. She said that there has also been criticism of the fact that IOM committees sometimes have members with known conflicts of interest. She noted that GAO (U.S. Government Accountability Office) reports seemed to be more balanced. She wondered if there was room to suggest that VA commission a GAO report instead. Dr. Steele stated that the statute says if an agreement with IOM to conduct this type of review can not be reached, the Secretary may contract with another organization of similar stature and expertise. She was not sure what organization might fit this description.

Dr. Steele commented that, in addition to the issues discussed regarding the use of animal studies, the IOM reports had also been selective in which studies had been considered and presented. One clear example was its failure to incorporate information from epidemiologic studies of Gulf War veterans. For example, in Volume 4, the IOM reported on the rate of multisymptom illness in Gulf War veterans. In RAC-GWVI reports, the Committee has listed figures from seven studies with findings in both deployed and nondeployed veterans. Six out of the seven studies show an excess of between 25 and 30 percent of Gulf War veterans are affected by multisymptom illness, in comparison to nondeployed veterans. One study reported that excess to be in the range of 13 to 15 percent. The IOM report only provides figures from this one study, with no mention of other studies' findings. There were many other examples that could be provided.

Dr. Steele indicated that one positive aspect of the IOM reports was that their focus on occupational exposure research in other populations made them a good resource for this information. However, IOM had fallen short in considering all of the other areas of information related to Gulf War illness, the health of Gulf War veterans, and effects of exposures in the Gulf War.

Dr. Golomb questioned the quality and evidence reviewed by IOM and stated that she wasn't sure if the Committee should even recommend IOM prepare another report. She indicated that in a study of the anthrax vaccine, the IOM had found the vaccine to be inherently effective against all forms of anthrax. This was based on the fact that the vaccine targeted protective antigen, which was present in every form of anthrax. But Dr. Golomb noted that there was mouse data that directly contradicted this conclusion. The mice present an antibody response to protective antigen, but are completely unprotected to future anthrax exposures. There are no data in humans to support that the vaccine is effective against different forms of anthrax. In light of the fact that there was directly contradictory evidence on effectiveness but no supporting evidence, Dr. Golomb expressed her reservations about advising another report be prepared.

Dr. Steele indicated that she thought it would be possible to address Dr. Golomb's concerns in the recommendations. She then outlined several possible recommendations that were detailed in her slides and asked for discussion of the different options. Mr. Smithson commented that, if the Committee recommended that another organization produce a new report, it should identify this other organization. Dr. Steele noted that it was difficult to identify such an organization. Dr. Melling stated that the great advantage of staying with IOM was that it was identified in the statute. He suggested that a powerful recommendation would be to acknowledge the law and asked that it be properly applied. If the study is then done properly, it would be even more powerful because the IOM, in effect, would have to reverse itself. Chairman Binns agreed with Dr. Melling. He commented that Dr. Golomb's first point may be the "telling one." If IOM is a business for hire by government agencies, it is known that if you hire a consultant, they will produce a report that says what you want.

Dr. Bloom disagreed, stating that this was not true. As a co-chairman of the National Academy's report committee, he sees all IOM reports designated for review. The report committee goes to great lengths in selecting reviewers and monitors the reviews to ensure they have no conflict of interest in relation to the outcome of the report. There may have been problems with biased reports in the past. However, for the past four years while he has served as report committee co-chair, he has strictly scrutinized the reports for potential bias. In cases where it has been identified, he has advised that it be made explicit that certain members of the committee in question may benefit from the outcomes of the report.

Chairman Binns stated that he was pleased to hear this and expressed his appreciation for Dr. Bloom's effort to resolve this issue. Scientists who have served on IOM committees have certainly been honorable scientists. To the extent to which there has been this type of influence, he stated his belief that it was at

the staff level. He thought the statute did not envision that there could be another organization suitable for this process. And he did not view it as IOM's fault that this has happened.

Mr. Smithson commented that the proposed recommendations 1 and 2 were reasonable, as they simply require asking IOM to redo the studies based upon the requirements of the original public law passed by Congress. He indicated that recommendation 3 was open to debate.

Dr. Bloom stated that the text that followed these recommendation bullets would have to state the problems related to VA's commissioning the reports in a way that did not match the requirements of the public law. Dr. Steele indicated this was addressed in the text of the chapter. That text laid out the facts described in her presentation, and was followed by the recommendation bullets. Chairman Binns stated that he thought it could be made clearer that VA, in contracting with IOM, did not commission reports that were in accord with the statute. Dr. Bloom stated that there was great discussion about the statement of task whenever a proposal comes to the IOM. These statements of tasks are listed against the recommendations made by the committees. If the recommendations don't match the statement of task, the report can not pass review.

From her review of the list of panelists and reviewers on these reports, Dr. Steele indicated that she was stricken by their lack of involvement in, and probably lack of familiarity with, the Gulf War illness research literature. She wondered if this was done on purpose. The reports appear impressive at first glance, owing to the volume of information described. So even reviewers who are great scientists, but know little about the information not considered, might conclude that the findings were "kosher." Dr. Bloom stated that while they are not specialists in this area, the reviewers should be wise enough to appreciate the facts.

Dr. Bill Goldberg, the Committee's designated federal officer (DFO) was asked for his thoughts on a possible recommendation to reassign responsibility for commissioning these reports away from VA's Office of Public Health and Environmental Hazards (OPHEH) to VA's Office of Research and Development (ORD). Dr. Goldberg stated that his reading of the statute was that the intent of these reports was to advise the Secretary on issues such as clinical care, benefits, and service connection. These issues are clearly outside the purview of ORD. ORD also would not have the funds to commission these reports, and the funds could not be transferred as they were part of the clinical appropriation. He stated that there were legal, contracting, and appropriation reasons why this transfer could not happen. Dr. Steele asked if it could happen if the funds were appropriated to ORD. Dr. Goldberg stated that it was a benefits issue, and the monies for benefits and clinical care could never be moved to ORD. He stated that the law would have to be rewritten to provide for this transfer and change in purpose. Dr. Steele commented that, in reality, the IOM reports were used for much broader purposes, and noted the fact sheet prepared by OPHEH for Senators Murray, Rockefeller, and Bond.

Chairman Binns commented that Dr. Goldberg's point was very interesting. He stated that one of the central problems was that OPHEH, on its own initiative, had begun to usurp the role of ORD and treat these reports as something to be used much more broadly than advice related to benefits. For example, the Secretary had recently been asked by several senators about the recent studies done by Dr. White and her team in Boston. The response, which was drafted by OPHEH, indicated that they were going to refer these questions to IOM, "which is the body that reviews Gulf War health studies for VA on a biannual basis." Chairman Binns stated this letter basically said that VA was going to use IOM, and didn't acknowledge that Congress had already established a body, i.e., the Committee, to advise on Gulf War research. He appreciated that Dr. Goldberg and ORD were not able to act on this. However, if the Committee did not address this situation, it might as well say it was wasting its time here. Somebody at VA had decided to use IOM, instead of the Committee, to advise on Gulf War research. This was not

right, nor what Congress intended. He thought, therefore, that the last recommendation should be included, with careful wording.

Dr. Haley asked if it could be worded so that when OPHEH issued these contracts for research reviews, it was with the concurrence of ORD. Dr. Steele commented that she wasn't sure why this process could not be removed from OPHEH. The statute may state the purpose is to advise on benefits. However, the information being reviewed is research. Chairman Binns indicated that he thought Dr. Goldberg's understanding of how VA budgeting operated was accurate. He thought that, in the worst case, the language could advise to move the contracting responsibilities out of OPHEH and suggest that the process should be concurred by ORD.

Dr. Haley thought there could be a distinction between contracting for the reports and the task of creating the charge to IOM. The contracting authority could stay in OPHEH. However, the charge could be written by ORD and given to OPHEH to go into the contract. Dr. Goldberg stated that ORD reports to the Secretary. OPHEH does as well. Each of the offices' charges come from "on high." ORD could not tell another office how to operate their shop. And OPHEH could not tell ORD what it should be funding in research. If OPHEH gets questions, they might request input from ORD on what research was being funded and occurring. They could get as much or as little input from ORD as they requested in drafting the Secretary's response. Dr. Goldberg recalled the inquiry by Senators Murray, Rockefeller, and Bond. He stated that input was requested from ORD related to what was happening in research. OPHEH's role in the organization was to write the response for the Secretary's signature.

Chairman Binns noted that, at the very least, the Committee could recommend that this role be taken away from OPHEH. Mr. Smithson stated that if this recommendation was made, the Committee should recommend the office to which it would be reassigned. Chairman Binns stated that the most that could perhaps be done was require the concurrence of ORD, but this might not be enough.

Dr. Golomb asked if it would be better to have no reports from IOM, rather than have a report that leads people astray. Chairman Binns stated that he believed the IOM would do a proper job if properly tasked.

Dr. Melling stated that a recommendation to move the study out of IOM would leave the door open for bureaucratic haggling and lack of progress. It would be better to stay within the envelope of the law. He wondered if it would be appropriate, as the Committee reports to the Secretary, to offer the Committee's service to review the charge made to IOM and then advise the Secretary whether or not the charge fulfills the requirements of those public laws. Chairman Binns indicated that this offer had already been made. When it was convenient for OPHEH to say this wasn't research, they were perfectly happy to say "we don't advise on your work." However, OPHEH will then take the position that they are the final word on research. Chairman Binns thought it would be great if such a provision could be made because it was certainly research, at least research that would be used for evaluating benefits. Mr. Hardie noted that was certainly the case because both Congressional directives, the one establishing the Committee and the one directing the IOM reviews, were created under the same law. Dr. Bloom asked why the Committee did not stipulate the statement of task for the next IOM study in the Committee's report. Chairman Binns stated that it was not clear what the next study was and noted that task statements were not trivial documents.

Dr. Steele asked what the consensus of the Committee was in relation to the contracting of future IOM studies. Mr. Smithson stated that if it was removed from OPHEH, there should be a recommendation as to where this authority should be transferred. Dr. Steele asked what would happen then if a suggestion to move it to a particular office was not possible. Mr. Smithson understood this, but thought a specific recommendation would be helpful in order for the Secretary to make it happen. Chairman Binns thought

it could be recommended to the Secretary that the responsibility should be removed from OPHEH and reassigned. Dr. Steele asked if he meant that the reassignment be made "as determined by the Secretary." Chairman Binns said the language could be fine-tuned, but just needed to make clear that the responsibility be removed from OPHEH. He would also support the idea of adding language that would allow the Committee to review the task statement.

Dr. Meggs asked if the Committee should be a little bit stronger in its explanation as to why, that is, because OPHEH did not properly charge the IOM with regards to the requirements set forth by Congress. Chairman Binns stated that he thought Dr. Bloom had made this point and agreed that the Committee needs to be clear that the fault lies with VA.

Mr. Hardie stated that he found it unacceptable that the Committee was not involved in the contracting with IOM, since the Committee was supposed to be determining and evaluating Gulf War research and was created under the same law. He hoped that this language was strong and forceful with regard to that message and that the Committee should be active in the process of creating future task statements. Mr. Smithson stated that the specific examples of what had been done should be included to remind them of this.

Dr. Steele asked if other members would like to address the questions raised, but none had additional comments. Mr. Smithson asked for clarification about whether the second recommendation was that the previous IOM reports be redone. Dr. Steele indicated that the general consensus had been yes, that this was the case. Dr. Golomb reiterated her reservations about reassigning it back to IOM. Even if one removed individuals with overt bias, the previous work will still influence the outcome. Dr. Bloom agreed that there was some truth to this. Chairman Binns stated that, between the awareness of this issue within IOM and a true change in policy at VA, he thought this was a solvable problem. Nothing has been solved to date, however. But for the recent letter drafted by OPHEH, he would have hoped it had been.

Dr. Melling asked to be reminded if there was a recommendation with respect to treatment issues. He acknowledged Dr. Haley's statements during the previous day's meeting that there was little point to pursuing serendipitous work in his program with the hope that some treatment will emerge. However, we know that good things happen by accident. The Committee should consider a recommendation that would improve the chances of capturing something good that does happen. Dr. Steele noted that the report discusses the two avenues of finding treatments. One is tied to physiology. The other one, which she did not view as being serendipitous, related to identifying and evaluating treatments in use for Gulf War illness or conditions with similar features. Overall, the draft report recommends that research leading to treatments receive the highest priority and that both approaches be utilized in identifying treatments.

Chairman Binns asked to return to the discussion about Dr. Golomb's recommendation to include advice that Gulf War veterans avoid pesticides. It is better to avoid pesticides, given what is now known versus what is not known. While the Committee has recommended that studies should be done on this and it has been explained in the text, it had never been included in a recommendation. Dr. Steele asked about the type of recommendation that might be made. For example, would the Committee recommend that VA advise their clinicians to advise ill veterans to stay away from chemicals? This was not a research recommendation and there were no data to support that clinicians do this. Dr. Golomb stated that there was data in an Australian study linking pesticides to ALS, and Gulf War veterans have an increased chance of getting ALS. Dr. Steele noted that there might be a lot of diseases that could be related to a lot of exposures that Gulf War veterans may have. She didn't disagree that this could be true, but there weren't data to support any of them in particular. Dr. Golomb understood, but noted that there was no expected health benefit from pesticide exposure but there were potential health harms. Even in the

absence of the anecdotal information where people say exposures make things worse for them, one could say that strong evidence is pending, but avoidance might be prudent. Dr. Golomb added, however, that she did not feel strongly that such a recommendation should be made, since she understood that the Committee was tasked to make research recommendations. But she indicated that if she was a sick veteran, she would want to know this.

Mr. Hardie stated that he was disappointed that OPHEH had failed to provide real information to Gulf War veterans. The information that has been provided has been a whitewash and/or contains nothing of substance. The coverage of the Committee's activities was limited. He noted that the most recent coverage only noted, in a paragraph, that new members had been appointed. It would be helpful if a real publication, one that did not imply that there was nothing wrong with Gulf War veterans, was produced by some other entity, a publication that veterans could take to their physicians. It didn't have to make judgments about the research. It just needed to present it. Why not have research summaries and citations for the studies? Why can't the Committee advise VA on what to do with the research that the Committee is reviewing?

Chairman Binns commented that there was a Committee recommendation that the clinical guidelines be revised and updated in light of research. He wondered if the Committee should restate this in the report. Mr. Hardie stated that he was thinking of a recurrent publication. Dr. Steele stated that she had never heard positive comments from veterans on the Gulf War Review or indications that it helped with their knowledge of Gulf War illness. She noted that only one edition had been published in the past year, and it had been online, and few knew how to find it. She wondered if the suggestion should be made that VA have a publication that does provide this service to veterans and does disseminate research. She asked how other committee members felt about this. Mr. Smithson stated that this would fall under outreach, and he had no problem with making such a recommendation. Chairman Binns stated that if the guidelines were revised, the veterans would be advised as well. Dr. Steele noted that the Committee's website provides summaries of the most current Gulf War research, and is regularly updated. This had been how the Committee had provided this information to the public. She hoped that the Committee's report would help in providing a comprehensive view of the subject in a way that a newsletter can't.

Mr. Hardie thought it was important to disseminate this information to treatment providers and veterans. The Secretary could determine how this dissemination should occur. Chairman Binns asked if Mr. Hardie thought revised treatment guidelines would take care of this and would provide an even more emphatic statement than a newsletter. Dr. Steele noted that there were also continuing education instruction materials on Gulf War health issues for VA healthcare providers, and the Committee had recommended that these be revised too. Mr. Hardie noted that the VA's webpage on Gulf War illness was poor, containing many broken links and a lot of information about the current conflict veterans and depleted uranium. There was little information that could inform a treatment provider. Dr. Steele said that she agreed that these types of improvements were needed, but the question was what the best way was to make this happen. Mr. Hardie indicated that the Committee should think about what would be the best approach to achieving this goal.

Dr. Steele asked the Committee to make note of any objections, additions, or other suggestions related to restructuring or rewriting the draft report that would be distributed in hard copy for review.

Chairman Binns stated that he had summarized the previous day's discussions of the UTSW program after the meeting. He said that there were some conflicting comments and his summary was not in the form or nature of recommendations. But there might be some value in presenting a summary of what individuals thought had been the most important points. This would provide comments in some official form to UTSW. He indicated that he would send these notes around for the Committee to review. If they

were accurate, they could be included as cover comments, along with individual comments provided by each Committee member.

Update on VA Gulf War research programs

William J. Goldberg, PhD
VA Office of Research and Development Gulf War Research Portfolio Manager

Dr. Goldberg gave the Committee an update on the Gulf War tissue biorepository. Dr. Louis Fiore, the principal investigator on the biorepository project, reported to Dr. Goldberg that ten brains of veterans with ALS had been "captured" from the ALS registry. Dr. Goldberg stated that he had asked Dr. Timothy O'Leary, Director of ORD's Clinical Science and Biomedical Laboratory Research and Development services, whether the program was in a position to begin accepting consents for brains and other tissues from Gulf War veterans. Dr. Fiore had indicated that they were ready, noting that the project had received institutional review board approval. Dr. O'Leary had requested the Committee's advice on systematic approaches to the identification of veterans and veterans' families that were willing to participate in this program and how to contact these individuals. This would be the specific recruitment of ill Gulf War veterans.

Dr. Steele noted Mr. Hardie's suggestion of a newsletter that is distributed periodically to Gulf War veterans.

Dr. Haley suggested going back and calling all of the veterans who participated in their national survey. There would be prospective data, collected over time, along with veterans' profiles. Dr. Goldberg asked if it was possible to incorporate this inquiry into the UTSW survey. Dr. Haley thought it was, considering the consent issues had been worked out. Dr. Goldberg stated that there would have to be care to ensure that the proper actions or links were in place to obtain the tissues once the veteran died.

Mr. Hardie asked if there was a national healthcare provider organization that could help identify veterans at the hospital level. Dr. Goldberg stated that this was difficult because most would probably not die at a VA hospital, so it wouldn't be a matter of having this consent in their VA medical records.

Dr. Haley stated it had to be a veteran and family issue. These veterans often die unexpectedly so there is no one at the hospital to coordinate this donation. It has to be the veterans and their families who work out a plan to contact the registry when the veteran dies. It would be like carrying a tissue donation card in their wallet. Dr. Goldberg stated that he would also speak to Dr. Fiore about the possibility of including the question in Dr. Haley's survey. Dr. Haley stated that this did need to be discussed because the highest yield would be those who had been in a survey. They had systematic health information about each veteran. Dr. Haley noted that there were potentially thousands of participants with 10,000 in his study, 10,000 in Dr. Kang's study, as well as Dr. White's Fort Devens' group.

Dr. Steele suggested contacting all of the veterans enrolled in the VA's Gulf War registry.

Dr. White commented that there were questions about whether institutional review board approval would allow her to go back to the Fort Devens' cohort for contact information. This action would probably require approval because they would be re-accessing names. The other issue was that contacting individuals about this type of donation is very tricky. This project involved the entire country and required a carefully thought-out program in place that specified how to approach individuals and what instructions would be given to the donors. Dr. Goldberg stated that the collection procedures had been worked out for the entire country. Dr. White was glad to hear this.

Dr. Steele asked if an announcement could be sent to the registry participants in the Gulf War Review and/or another type of publication. This would potentially reach 150,000 Gulf War veterans. Mr. Smithson noted that mailings were not being sent at this time. Dr. Steele commented that it could be done for this specific purpose. Dr. Goldberg stated that it was his understanding that the Gulf War Review would be sent out in paper and electronic format in the future. Dr. Steele said that Dr. Mark Brown had told her that the Gulf War Review would remain an online publication. Mr. Smithson asked Dr. Goldberg if he knew when it was slated to be mailed out to veterans. Dr. Goldberg stated that he would have to check when he returned to Washington, D.C. Dr. Steele noted that this would be a reason to mail out the newsletter, which could include updates on other issues.

Mr. Hardie commented that DoD had an excellent mailing list, noting that it had been used to notify many Gulf War veterans of their possible exposure to the debris plume from the demolition of the Khamisiyah ammunition depot.

Chairman Binns invited veterans to comment on possible ways to notify the veteran population of this opportunity.

Ms. Nichols suggested that the VA put this information on its website and issue a public service announcement and press release about the program. She also suggested asking the veteran service organizations to include this announcement in their magazines. This would at least reach those veterans who have access to the Internet.

Mr. Hood stated that veterans had an organization called Dignity Memorial that could distribute this message. Notices could be included in medical journals to notify civilian physicians of the program. Public service announcement also could be made by veterans service organizations and the Department of Health and Human Services. There are three categories of veterans to contact, both active and inactive: Reserves, National Guard, and Active Duty.

Dr. Goldberg indicated that he would take these suggestions back to Dr. O'Leary and would report at the next meeting on this effort's progress.

Dr. Steele asked Dr. Haley for clarification about his tissue bank. Dr. Haley stated that it would be a blood and DNA bank, not a brain bank. There would be no overlap with the Gulf War veteran biorepository.

Dr. Steele asked Dr. Goldberg for an update on funding of Gulf War research proposals. While there was no longer a specific Gulf War funding announcement, she wondered how many proposals were being submitted via the normal funding routes. Dr. Goldberg stated that no newly submitted projects had been included on the portfolio lists that the Committee received. He stated that there were a couple of studies that would begin this year, but that they had been included on the previous year's funding list. Most of the proposals being received were focused on OIF/OEF. A significant portion of VA's research budget had been appropriated to the UTSW program. There was also significant pressure from Congress and the Secretary's office to address OIF/OEF issues. There was a need for VA to move into this realm.

Dr. Steele asked about the progress in listing Gulf War studies on NIH's website: www.clinicaltrials.gov . Dr. Goldberg stated that other work had sidetracked him from this project. However, he would take steps to "put it back on his plate." It wasn't an issue of whether studies other than clinical trials could be included on the website. Any studies that involved human subjects could register and use the website as a source of recruitment. Dr. Steele noted that the Committee hears from veterans all the time that they

would like to participate in studies. She said that there were three clinical trials involving Gulf War veterans currently listed on the website. One involved cognitive behavioral therapy administered using a telemedicine approach. Another was a clinical trial of treatment for irritable bowel syndrome. The last one was an evaluation of the use of continuous positive airway pressure machines to treat sleep irregularities in Gulf War veterans. Dr. Goldberg stated that there were several other studies that involve human subjects, but were not trials. Imaging projects fall into this category. They are not required to be registered, but can be.

Chairman Binns thanked Dr. Goldberg.

Public Comment – Day 2

Chairman Binns explained to those present that he had limited earlier discussion of the recommendations to Committee members because this was a particular Committee function. He indicated that the Committee now would like to hear comments from the recommendations or other matters. He asked how many individuals wished to speak and noted that comments should be limited to five minutes.

Dr. McGill spoke to the Committee. She discussed her website honorthenames.com. One of the purposes of the website was to use it as a research tool. She requested help in making it complete. They have the names of 4,500 deceased veterans. This also raised the issue of surveillance. She noted that the life expectancy of Vietnam veterans was 57 years. One of her reasons for starting the website was to try and determine the life expectancy of Gulf War veterans, as well as their causes of death. They were still working on this and would be for the rest of their lives. She recommended that there be "cross-talk" between this website and the Committee's website. She indicated that she would ask her webmaster to include a link to the Committee's website. She requested that the Committee do the same. With regards to the IOM study, Dr. McGill stated that the IOM aimed their reports toward their customer's request. She asked that an ill veteran be placed on the IOM committee to help correct the problems that were made in the IOM's first six volumes on Gulf War health.

Chairman Binns thanked Dr. McGill.

Mr. Mark Anderson, whose brother-in-law served in the first Gulf War, spoke to the Committee. He thought that the Committee was generally doing a good thing, but asked it to not lose sight of the issue of depleted uranium. It was the one constant in the war, which was arguably among the most brutal wars in history, waged against third world nations with little military to speak of and killing over one million Iraqis in the most inhumane fashion. Most in the United States can not even imagine what is happening there. Mr. Anderson quoted Mr. Mitchel Cohen's statement that "300 tons of depleted uranium from spent rounds lay scattered in various sizes and states of decay across the battlefields of Iraq and Kuwait. Welcome to the wave of the future: 'low intensity' nuclear war, inaugurated in the Gulf War by the United States."

Mr. Anderson noted that in a survey of 10,000+ Gulf War veterans, 82% had entered captured Iraqi tanks that were disabled by depleted uranium rounds. Quoting Mr. Cohen again, Mr. Anderson stated: "Leaving more than 600,000 pounds of depleted uranium scattered throughout the region, by war's end the US had turned the Gulf area into a deadly radioactive grid, affecting not only US soldiers but hundreds of thousands, perhaps millions, of people who live and work in the Gulf. . . . Is it any wonder that many symptoms of Gulf War Syndrome are so similar to radiation sickness? . . . A secret report by the British government estimated that the use of depleted uranium weapons in the Gulf could alone account for 500,000 deaths in the region. That report was based on estimates that 25 tons of depleted

uranium munitions had been used; in actuality, the Department of Defense now estimates that the US fired more than 12 times that amount." Mr. Anderson stated that we were in a unique situation because we now live in perpetual warfare. There appears to be no resolution in sight. We have been using these munitions in the Middle East for close to two decades, in varying degrees. Mr. Anderson's point was that sick and injured veterans would keep coming. This will cause the cost of the war to "balloon." Every dollar spent on the ongoing war will deplete the funds that might be available for research. Mr. Anderson suggested that Committee members think as citizens, not in their specialized roles as scientists. Do we as American citizens like this kind of policy? Ultimately, to stop Gulf War syndrome, we must stop the Gulf War.

Chairman Binns thanked Mr. Anderson.

Mr. Hood commented that his occupations while serving in the Gulf were the same ones he had stateside, that is, he had been an air surveillance technician, combat plan technician and computer technician. When he deployed, he deployed as a one man team as an operations control technician. He described his service in the Gulf and health conditions following this service. He learned during his time in the hospital how to do post-deployment interviews and began to work with a South Texas group that operated out of the Veterans of Foreign Wars office in San Antonio. He spent his time checking on his comrades during this time and learning about the various exposures that they had been subjected to. Mr. Hood said that Mr. Kirt Love had given him ideas that he incorporated into his questionnaire. They also hand out maps of biological and chemical weapons sites, SCUD and nuclear reactor sites, as well as areas where depleted uranium was known to be used. He noted that, like in the movie "Hidalgo", the desert moves like a rolling carpet. So, when one starts talking about Gulf War illness, one must considered 970 nuclear, chemical, and biological sites that were hit during the first 45 days of the war. Those who moved in during the ground war were "slammed." They moved up into the toxic zone. After the ground war, 994 additional sites were demolished during the cease-fire phrase with troops in place. Khamisiyah represents one of those 994 sites. There were 40 warehouses and 100 bunkers, approximately the size of Wal-Mart. Mr. Hood asked if anyone would like something like this blown up in their backyard.

Chairman Binns thanked Mr. Hood.

Ms. Lauren Billings, an Air Force Gulf War veteran, spoke to the Committee. She stated that there were 90 aviators within her unit. Within one year of their return from the Gulf, there were four cases of cancer: prostate (1), bone (1), breast (1), and cervical (1). This amounted to four individuals out of 90 within the first year. Ms. Billings questioned whether these statistics were the same as the general population.

Chairman Binns thanked Ms. Billings.

Ms. Denise Nichols spoke to the Committee. She stated that the diagnosed illness data were not being collected. She recalled the 1991-1994 cancer information that she had submitted to the Committee in May 2006. She stated that she had asked the Committee to request the data on Gulf War veteran cancer deaths. The only way to get compensation like Agent Orange veterans is with a presumption of illness. Gulf War illness is separate from diagnosed illnesses. However, some Gulf War veterans have both. The only Committee that Gulf War veterans have is this one. VA didn't follow the Committee's recommendation to create another committee to address clinical and benefits issues. She hoped that this recommendation could be carried forward in the report. The Gulf War veterans are feeling the same as Vietnam veterans did. Every time one opens their paper or e-mail, there is another benefit for the OEF/OIF veterans. Ms. Nichols stated that she receives calls from Gulf War veterans asking for a progress status report and indicating to her that they still need help. She keeps standing up, even though she is told to shut up, about this issue. She had received an e-mail that General Downing, who

commanded the American Special Operations forces during Desert Storm, passed away the previous day from multiple myeloma and bacterial meningitis. She noted that a Gulf War veteran with ALS recently passed away too. With regards to environmental medicine, she did not receive answers from VA and sought her own answers and testing so that she could pass this knowledge onto others. She discussed the various types of testing and treatments that she had undergone. These involved nontraditional medicine and IVs of vitamins and supplements, including glutathione and CoQ10. It wasn't a whole lot to ask that these treatments be considered. It helped her. It wasn't a cure, but it did help with cognitive function.

Ms. Nichols also commented that she received calls from veterans whose health had stabilized, but then moved and began having problems. Some were exposed to agricultural chemicals and became unstable. She can only tell them that there is no treatment, but she tries to help them figure out the triggers for their new health concerns. And the only option is to try and get away from it. She uses this as a complementary medical approach. Lastly, Ms. Nichols wanted to ask the Committee to remember to suggest investigations of blood hormones—pituitary and adrenal hormone levels in Gulf War veterans. If abnormal values are found, the veteran should receive treatments. Many veterans are on hormones and it helps them.

Dr. Steele said that she understood that Ms. Nichols was frustrated about not getting information on rates of cancer and diagnosed illnesses. Dr. Steele noted that one of the recommendations presented at the Committee's last meeting was to monitor cancer rates. The Committee's report quotes the rates that have been reported from different studies and notes that these rates are pretty dated and are not complete. But the rates are probably more complete than those that could be obtained from VA hospital data. However, it is still not good enough. The Committee continues to recommend that more comprehensive data collection be done to monitor cancer rates in Gulf War veteran. A few questions have been raised by results from the state cancer registry study, which is ongoing. Dr. Steele noted that this issue hasn't been ignored, but more needs to be done.

With respect to the other diagnosed illnesses, Dr. Steele stated that the Committee has emphasized the need to identify rates of neurological diseases. However, the hope is that the large surveys will help identify any problems that have not yet been identified, perhaps with regards to autoimmune diseases, etc. If a "red flag" is raised, the Committee could then make more specific recommendations. This will require an epidemiological study to ascertain whether there is really a problem. Monitoring hospital or benefits data is inadequate because it would only tell us if there was a "huge" rate of illness, and maybe not even then. For example, if one looked at the benefits data for MS, one would find no difference between deployed and nondeployed Gulf War era veterans. But this does not really tell us if there is an excess rate, since we have no idea whether those who have separated from the military and later developed MS would have applied for VA benefits. This is why an epidemiologic study is needed. Dr. Steele stated that her Kansas study had identified a number of Gulf War veterans who had been diagnosed with lupus since the war. But it was not enough cases to evaluate statistically to determine if there was an excess.

Dr. Haley commented that his group would be looking at adrenal and pituitary hormone levels in its Gulf War study.

Ms. Nichols asked that the Committee's report highlight the need to look at oxidative stress and autoimmune disorders. Dr. Steele stated that the recommendation is to look at all medical conditions, including those.

Mr. Hood asked if any of the researchers present had utilized the Armed Forces Institute of Pathology (AFIP) tissue and blood bank samples. He stated that he was registered in this system and that this would be a good resource for study.

Chairman Binns thanked the veterans present. He expressed his appreciation for what many of the veterans were doing to try to make their own bodies and tissues available for research, as well as their participation in meetings like this. He knew it was difficult to stand up and talk about it, but the Committee did appreciate it.

Chairman Binns expressed his appreciation for the Committee's participation and the hospitality of UTSW. He noted that there was considerable talent and attendance at the previous day's meeting and this was a sign of the UTSW program's commitment to do the job that they have assumed.

The meeting adjourned at 1:47 p.m.