Research Advisory Committee on Gulf War Veterans' Illnesses

November 6-7, 2006, Committee Meeting Minutes

U.S. Department of Veterans Affairs
Dallas, TX

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 November 6-7, 2006, meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses.

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

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Attendance Record

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

Committee Consultant
Jack Melling

Committee Staff
Barbara LaClair
Laura Palmer

Guest Speakers
Ilya Bezprozvanny
James Bibb
Richard W. Briggs
Kathleen Considine
George N. DeMartino
Louis Fiore
William Goldberg
Robert W. Haley
Vince Iannacchione
Joel Kupersmith
Anil R. Prasad
Christopher Sinton
Jeffrey Spence
Philip W. Thomas

Abbreviations

AChE	Acetylcholinesterase
AFIP	Armed Forces Institute of Pathology
ALS	Amyotrophic lateral sclerosis
CCEP	Comprehensive Clinical Evaluation Program
CDC	U.S. Centers for Disease Control
CDMRP	Congressionally Directed Medical Research Programs
CRADO	Chief Research and Development Officer (VA)
CRH	Corticotropin-releasing hormone
DoD	U.S. Department of Defense
EEG	Electroencephalogram
FAQ	Frequently asked questions
fMRI	Functional magnetic resonance imaging
FY	Fiscal year
GWI	Gulf War illness
HDR	Health data repository
HPA	Hypothalamic-pituitary-adrenal axis
IOM	Institutes of Medicine
IRB	Institutional review board
IRS	U.S. Internal Revenue Service
KTO	Kuwaiti Theater of Operation
MOS	Military occupation specialty
MS	Multiple sclerosis
NBC	Nuclear, biological and chemical
NCI	National Cancer Institute
NIH	National Institutes of Health (US)
NTE	Neuropathy target esterase
ORD	Office of Research and Development (VA)
PB	Pyridostigmine bromide
PTSD	Posttraumatic stress disorder
RAC-GWVI	Research Advisory Committee on Gulf War Veterans' Illnesses
RFA	Request for applications
RTI	Research Triangle Institute
SAS	Statistical analysis system
SPECT	Single photon emission computed tomography
UK	United Kingdom
UT Southwestern	University of Texas Southwestern School of Medicine
VA	U.S. Department of Veterans Affairs

VHA	Veterans Health Administration (VA)
VHI	Veterans Health Initiative
VSO	Veteran service organization

Agenda

November 6-7, 2006

Monday, November 6: Meeting Held in the Community Center
Dallas VA Medical Center
4500 South Lancaster Road
Dallas, Texas

[Please Note: The meeting will be held in a different location Tuesday, Nov 7]

Monday, November 6

8:30 – 9:00	**Informal gathering, coffee**	
9:00 – 9:15	**Welcome, introductory remarks**	**Jim Binns, Chairman** **Res Adv Cmte Gulf War Illnesses**
9:15 – 9:45	**Overview of Gulf War-related research at the University of Texas Southwestern Medical Center**	**Dr. Robert Haley** **Univ of Texas Southwestern**
9:45 – 11:00	**Epidemiologic research:** **National Survey of Gulf War-Era Veterans**	**Kathleen Considine** **Vince Iannacchione** **Research Triangle Institute**
11:00 – 11:15	**Break**	
11:15 – 11:30	**Statistical innovations to increase sensitivity of group comparisons in brain imaging: An update**	**Dr. Jeffrey Spence** **Dr. Patrick Carmack** **Univ of Texas Southwestern**
11:30 – 12:30	**Neuroimaging innovations to detect subtle alterations in brain function**	**Dr. Richard Briggs** **Univ of Texas Southwestern**
12:30 – 1:30	**Lunch**	
1:30 – 1:35	**Introduction to preclinical studies leading to rational development of treatment**	**Dr. Robert Haley**

Agenda
Monday, November 6 (cont.)

1:35 – 2:00	**A rodent model of Gulf War illness: Development and validation**	**Dr. Christopher Sinton Univ of Texas Southwestern**
2:00 – 2:30	**Altered signal transduction as a factor in Gulf War illness**	**Dr. James Bibb Univ of Texas Southwestern**
2:30 – 3:00	**Organophosphates and the structure and function of the ubiquitin-proteasome**	**Dr. George DeMartino Dr. Philip Thomas Univ of Texas Southwestern**
3:00 – 3:30	**A neuronal cell culture model for the study of Gulf War illness**	**Dr. Ilya Bezprozvanny Univ of Texas Southwestern**
3:30 – 3:45	**Break**	
3:45 – 4:45	**Approaches to assessing treatments for Gulf War illnesses: the Southwestern experience**	**Dr. Robert Haley**
4:45 – 5:45	**Committee discussion of Gulf War-related research at U.T. Southwestern**	
5:45 – 6:15	**Public questions/comments on scientific presentations**	

Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses
November 6-7, 2006

Tuesday, November 7: Meeting Held at the Dallas/Fort Worth Airport Marriott-North
8440 Freeport Parkway
Irving, Texas

Agenda

Tuesday, November 7

8:00 – 8:30	**Informal gathering, coffee**	
8:30 – 9:30	**Update on recently published research relevant to the health of Gulf War veterans**	**Dr. Lea Steele** **Res Adv Cmte Gulf War Illnesses**
9:30 – 10:30	**Report on Gulf War Tissue Repository**	**Dr. Louis Fiore, VA Boston** **Dr. Anil Prasad, VA Tucson**
10:30 – 10:45	**Break**	
10:45 – 11:00	**FY2006 Gulf War research expenditures**	**Dr. Lea Steele**
11:00 – 11:30	**Update on VA Gulf War research programs**	**Dr. Joel Kupersmith** **Dr. Bill Goldberg, VA Office of Research and Development**
11:30 – 12:30	**Public comments**	
12:30 – 1:30	**Lunch**	
1:30 – 1:45	**Overview of Gulf War-related information on the RAC-GWVI website**	**Laura Palmer** **Res Adv Cmte Gulf War Illnesses**
1:45 – 2:30	**Committee business**	
2:30	**Adjourn**	
2:35	**Special briefing: The current status of research on Gulf War illnesses**	**Dr. Lea Steele**

Mr. Adrian Atizado and Dr. Hugh Tilson, Committee members, were not able to be present at this meeting. The meeting was held on Monday, November 6th, in the Community Center at the Dallas VA Medical Center, 4500 South Lancaster Rd, Dallas TX. The meeting was held on Tuesday, November 7th, at the Dallas/Fort Worth Airport Marriott North, 8440 Freeport Parkway, Irving, TX.

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 9:01 a.m. He welcomed Committee members, University of Texas Southwestern School of Medicine (UT Southwestern) presenters, Department of Veterans Affairs (VA) Office of Research and Development (ORD) staff, veterans and other members of the public. He extended his thanks to the Dallas VA Medical Center for hosting the day's meeting. The Committee members introduced themselves and give a brief description of their background for the benefit of the audience. Chairman Binns commented that Mr. Adrian Atizado and Dr. Hugh Tilson were not able to be present. He noted Dr. Tilson was giving the keynote lecture, as well as receiving the Wade Frost Hampton award, the next day at the American Public Health Association's annual meeting in Boston, MA.

Chairman Binns stated that the agenda for the meeting was excellent and thanked Drs. Lea Steele and Robert Haley for organizing an impressive group of speakers. He wished to use this time to comment on two developments that had occurred since the Committee's August 2006 meeting, which represented the highs and lows of Gulf War illness (GWI) research. The first development was the release of an Institute of Medicine (IOM) report that was widely publicized as having proved that there was no such thing as Gulf War illnesses. Chairman Binns noted that the IOM actually concluded that there was no unique syndrome because other people have chronic multisymptom illnesses. However, he believed that the problem with this report was deeper than a poor choice of words. The report missed a lot with respect to what is known about Gulf War illnesses. It missed a lot because the VA staff who ordered the report limited the evidence that could be considered, excluding some very important categories of evidence. He noted that the staff in question were not within VA's ORD. He asked the Committee and audience to consider how far the Committee would get if it: (1) was not allowed to consider any animal studies or government reports, such as the 2003 Department of Defense's (DoD) report on pesticides; or (2) only had one day of outside presentations whose common theme was that these types of illnesses happen after every war. The IOM committee did not find much because the study was designed to not find much. In other words, Chairman Binns stated that it was "rigged." If one felt these words were too strong, Chairman Binns invited him or her to read his November 2005 Congressional testimony, which detailed how every IOM report on Gulf War illnesses had been "rigged" to exclude from consideration important categories of evidence that Congress expressly required. He found this to be despicable and observed that it was characteristic of the federal government's past approach to Gulf War illnesses research. He stated that he would leave this for now and concentrate on the future.

Chairman Binns stated that the other development of interest was DoD's recent funding announcement, a request for applications (RFA), in relation to the availability of $5 million for Gulf War illnesses research. This RFA was a direct result of the work of the Committee, beginning with its September 2004 report, in which it was recommended that Congress keep DoD in the Gulf War illnesses research "business." This was done despite the fact that DoD had zeroed out this line item in its budget. He noted that information on this program had been presented by COL Janet Harris, the director of the Congressionally Directed Medical Research Program (CDMRP), at the Committee's August 2006 meeting. He also noted that

copies of the RFA were in the Committee's binders and were located among the public handouts available at the back of the room. He stressed that this was an incredible opportunity and encouraged researchers in the audience to submit proposals and encourage colleagues to do the same. He noted that the RFA was focused on the study of treatments, specifically treatments that already exist, and diagnostic tests. It would support small, early-stage studies of treatments for which there is limited supporting evidence at this time or for which there are simply clinical observations. It is open to virtually anyone and proposals will be reviewed by a panel that is highly knowledgeable about Gulf War illnesses. Chairman Binns noted that four of the seven members of this review panel also serve on the Committee. He noted that there were two areas that were particular priorities for research interests: (1) "Identification and evaluation of currently available treatments: Funded projects may include observational studies, experimental studies, or a combination of methods. Possible methods may include retrospective and/or prospective outcomes evaluation, pilot trials, or other innovative designs for providing systematic information on treatment outcomes. Interventions to be evaluated may include conventional medical treatments or complementary therapies. However, a clear rationale must be provided for studies of treatments for which no preliminary evidence exists regarding their utility in treating GWI, GWI-related symptoms, or similar multisymptom conditions such as chronic fatigue syndrome and fibromyalgia."; and (2) "Identification of objective indicators of pathology that distinguish ill from healthy veterans: Priority projects will identify measures that can be useful as biomarkers for GWI and shed light on pathophysiological mechanisms potentially amenable to treatment."

The DoD RFA provided for two award mechanisms. The first mechanism was an exploration-hypothesis development award. "The intent of this award is to fund initial exploration of innovative, untested, potentially groundbreaking concepts aimed at identification of beneficial treatment interventions or potential treatment targets for GWI. Results of studies . . . may provide the scientific rationale on which a new hypothesis can be based . . . The award is designed to provide investigators with the opportunity to pursue serendipitous observations." Chairman Binns noted that these awards were for $25,000 to $75,000 in direct costs over one year.

The second award mechanism involved investigator-initiated research awards. "The intent of this award is to encourage basic or clinical research aimed at identification of beneficial treatment interventions or potential treatment targets for GWI." Chairman Binns noted that projects funded under this mechanism were eligible for $25,000 to $600,000 in direct costs for one to four years. He went on to say that the general thrust of this RFA was to encourage more studies at smaller dollar figures, instead of a few expensive studies. If researchers kept their proposals small and simple, they should have a better chance of having a proposal approved. As to who can apply, Chairman Binns noted that "all individuals, regardless of ethnicity, nationality, or citizenship status, may apply as long as they are employed by, or affiliated with, an eligible institution." Eligible institutions included "profit, nonprofit, public, and private organizations, such as universities, colleges, hospitals, laboratories, and companies. . . . Local, state, and federal government agencies are eligible to the extent that proposals do not overlap with their fully funded intramural programs." Chairman Binns stressed that Letters of Intent under this RFA were due December 1, 2006. However, the final proposals were not due until early February 2007.

Chairman Binns hoped that meeting attendees, especially those who have been with or followed the Committee for the past five years and who have seen the road blocks and obstacles of the past, saw this is as a unique document and this RFA should produce a good group of proposals and reviews. However, the word needs to be spread. Chairman Binns stated that was "our" job now. He encouraged all in attendance, especially those who might have an insight into a treatment that might benefit ill veterans with a safety profile that justifies the projected benefits, to focus on this RFA and promote it with any doctor or researcher. Chairman Binns stated that the fundamental purpose of the Committee, as well as the fundamental principle that is to guide federal Gulf War illness research, was not to publish papers,

hold meetings, or prepare testimony for Congress. It was to produce something that will make a difference to veterans' health. This is the chance to do this. He was very grateful to all of those who had contributed to making this RFA possible.

Chairman Binns asked those present to make a concerted effort to stay on track during the day's presentations so that discussion would not have to be shortened at the end. He stated that the key was having all of the presenters adhere to their allotted time limits. He suggested that each presenter reserve at least one-third of their time for discussion. He noted that Committee staff would be providing signals to each presenter to let them know how much time was remaining.

At that point, Chairman Binns turned the proceedings over to Dr. Robert W. Haley, a professor at UT Southwestern, for an overview of UT Southwestern's Gulf War illnesses research program.

UT Southwestern Research on Gulf War Syndrome: Summary and Program Overview

Robert W. Haley, MD
Professor, UT Southwestern School of Medicine

As Dr. Haley began his talk, he stated that he had hoped that the research funding contract between VA and UT Southwestern would have been signed by that day, or even that morning, but it had not come to pass. Dr. Haley commented that the negotiations had been excellent, involving VA ORD, VA's General Counsel, contracting offices at VA Central Office and Dallas VA Medical Center. It had been a good learning experience for everyone involved. He indicated that UT Southwestern was pleased with the contract development process and that he believed VA was too. However, as the contract had not been signed yet, the presentations over the course of the day would focus on UT Southwestern's previous and current research and conclude with some new ideas that the Committee should consider with respect to future research. He began the day's presentations by providing an overview of UT Southwestern's Gulf War illnesses research program. (See Appendix A – Presentation 1.)

Dr. Haley then introduced Ms. Kathleen Considine and Mr. Vince Iannacchione from Research Triangle Institute (RTI) International to provide information on the national survey of Gulf War veterans and nondeployed era veterans.

U.S. Military Health Survey

Kathleen Considine and Vince Iannacchione
RTI International

Ms. Considine, Project Director, provided an overview of the objectives and design of the survey, now called the U.S. Military Health Survey, but formerly known as the Survey of Gulf War-era Veterans. Mr. Iannacchione, Senior Statistician and former Project Director, discussed some of the survey's pilot data relating to demographics, comparisons of various Gulf War illness (GWI) case definitions, and comparison of the prevalence of GWI case definitions by troop location. (See Appendix A – Presentation 2.)

Following their presentation, Dr. Bill Meggs, a Committee member, asked if RTI had considered the possibility that someone might want to access and/or alter the data they were collecting and if so, what safeguards had they had implemented to prevent this. Ms. Considine stated that RTI's computer network had elaborate firewalls and secure, backed-up servers that, to her knowledge, had never been accessed from the outside. She noted that the data itself were also stored in a way that only the programmers

would be able to utilize. Dr. Meggs asked if similar precautions had been taken to prevent an "inside job." Ms. Considine acknowledged that there were different problems with internal security, but noted that only select RTI personnel had access to these servers. Mr. Iannacchione mentioned another possible mechanism by which survey data could be skewed, that being the telephone equivalent of a field interviewer who filled out the questionnaire himself because he didn't want to drive across town. Ms. Considine noted that to prevent problems of this type RTI had a silent monitoring system. The interviewers do not know when they are being monitored by the call center and/or project staff.

Mr. Anthony Hardie, a Committee member, noted that RTI was using a troop location database and asked how the study would then account for the unique experiences of Special Forces teams. He stated that those teams had been located deep in Iraq, working individually to identify targets. There also were two or three men Psych-Ops and Civil Preparedness teams that roamed, as well as some ad-hoc units created specifically for the Gulf War that were not formal military units, e.g., liaison units. Mr. Iannacchione replied that they were sensitive to the special nature of these troops, and acknowledged that they had limited success in identifying these individuals with the troop location database. He stated that they had done a previous study involving sampling of Nuclear, Biological, and Chemical (NBC) personnel and were able to identify some Army Special Forces, but that many military occupation specialty (MOS) codes had been blanked out. Dr. Haley added that considerable thought had been given to this critical issue and they were taking steps to ensure enough of these troops were included in the sampling plan. He acknowledged that the unit location database probably selectively excluded Special Forces. He explained that the questionnaire asked about the veteran's particular unit and the length of time the individual served with the unit. RTI would follow up by sending the respondent a map with coordinates to show where they were during the war. Ms. Considine noted, however, that the Special Forces were the least likely to identify themselves on the map during the pilot survey because their missions were classified. Dr. Haley agreed, but added that the survey respondents would be informed about the study's certificate of confidentiality. This was to encourage their disclosure of their location information, if they could. He stated that this certificate was a major issue in receiving approval by the military's institutional review board (IRB) on human subjects. This IRB required that the certificate of confidentiality be obtained so that the collected information could not be divulged, even to the military.

Dr. Floyd Bloom, a Committee member, asked if the consent forms for drawing the blood samples allowed for the retention of the samples. Dr. Haley indicated that they did. Chairman Binns asked if someone might elaborate on the blood tests to be conducted. Dr. Haley stated that the primary purpose was to look at the paraoxonase levels and genotypes for deployed and nondeployed veterans.

Dr. Daniel Clauw, a Committee member, noted that the study was starting with a particular bias, that Seabees were affected with Gulf War Illnesses at a different rate than other groups. He wondered if a higher proportion of Seabees would be selected to give serum or other samples than their representation in the general military population. Mr. Iannacchione indicated that this was the case. They will be looking at 592 Seabees, who will be roped into certainty strata. The probability of selection for Phase I and II, as well as the initial sampling weight, would be 1 and they hoped to achieve a good participation rate from these individuals. He added that they would contribute very little, in a weighted sense, to the population prevalence. They are more interested in getting a critical mass of these veterans so they can do a longitudinal follow-up. Dr. Haley noted that this was sort of a special study. Dr. Clauw stated that this was clear to him, but asked if it was a special, set-aside study or if these veterans would be combined with the general military population in the sample. Dr. Haley replied that if they were, their effect would be minimal because they would be weighted so low and wouldn't have much impact on the final results. Dr. Clauw stated that this should be true for the epidemiological study, but wondered if it could be appropriately corrected when oversampling for biological measures from certain strata. Dr. Haley stated that one would have to look at that stratum separately and that oversampling for Seabees would allow

them to look at longitudinal measures and check validity and selection biases from previous research. Mr. Iannacchione stated that they optimistically might expect 400 Seabees to participate, with some percentage of them agreeing to give blood samples. If 200-250 out of the 2000 blood samples were from the Seabees, they would comprise a noticeable proportion of the total blood samples. This is called, in sampling, an inefficiency. They would have to use weights to downsize the influence of Seabees in the population estimates, but because they are oversampled, there will be larger confidence intervals around these estimates. It is a trade-off.

Dr. Meggs asked if the contact information in this database would be available for recruitment by other investigators. Dr. Haley stated that this was one of the things that they would like to eventually do, i.e., encourage collaborative research using this database. One of the models they have is the Vietnam - Agent Orange twin database. Part of the design in this study is to see if they can create a similar twin database that would be available for studies on a wide basis. Dr. Haley stated that they hadn't studied the logistics of this yet, but this was the ultimate goal.

Dr. Mary Nettleman, a Committee member, asked if they would adjust for the "healthy warrior" effect in the nondeployed in the primary analysis. Mr. Iannacchione replied that they would. They will have two subgroupings among the nondeployed: (1) nondeployable for medical-related reasons; and (2) nondeployable for job-related reasons. The hypothesis is that the job-related group will be a surrogate for something that may have been going on, e.g., an individual was in a deployable unit and was transferred out before the unit was deployed. Part of the design authorization is to focus on comparison of the folks who were deployable but not deployed versus those who were actually deployed. Dr. Nettleman commented this might open the design to criticism because it takes the sick people out of the controls. Dr. Haley stated that this had been a major issue/focus in the planning of the study. First, they will provide all the information, looking to see if there are different syndrome case definitions represented at higher rates in deployed versus nondeployed, period. Then this information will be stratified to examine individuals' health before the war or for other reasons they might not have been deployed. The most defensible subgrouping is the "hardcore" medical nondeployed, e.g., those who were in the hospital or had a chronic illness before the war and that is the reason that they weren't deployed. They were clearly not like the individuals who were deployed since none of these individuals were in the deployed group. As for the job-related nondeployed group, Dr. Haley noted that all military personnel are considered deployable today but that this was not true in 1990-1991. There were several jobs that were not customarily deployed. These individuals never thought they would go and never did. This also applied to units. Dr. Haley said that they thought that some sick individuals were quietly transferred from units that were deploying and they might find an excess of prewar chronic illness in the job-related, nondeployed strata. The idea is to test the overall hypothesis and then lay out the conclusions. Dr. Nettleman commented that this was somewhat analogous to an "intent to treat" analysis. Dr. Haley agreed and noted that the control groups would be the nondeployed, but they would have the ability to sub-stratify. They put a lot of thought into how to measure this. They tried to get information from prewar hospitalization data, which are available, but the data were too sparse. Dr. Haley noted that DoD was now saying that the mid-1990s hospitalization studies were "garbage." He believes they now have their design in a nice, crisp format and intend to lay out their results so everybody can see what they find.

Dr. Nettleman asked if gender differences would be examined in the full study. Mr. Iannacchione stated that they didn't know yet what percentage of the survey sample would be female. They hoped to have this determined by the end of the month. Females could be part of dozens of the 58 domains being examined.

Dr. Nettleman asked how they were able to obtain the contact information from the U.S. Internal Revenue Service (IRS). Dr. Haley stated that there was a 1970s law that authorized government-sponsored

study/surveys involving environmental exposure questions to use IRS information. They were in the process of getting this information, which would greatly increase their ability to locate veterans. Dr. Haley added that this type of information was commonly used.

Mr. Smithson, a Committee member, asked when the pilot survey was conducted. Ms. Considine stated that it was conducted between January 2005 and April 2006. Mr. Smithson noted the May 2006 theft of VA electronic information and asked what RTI was doing to address veterans' concerns about this happening with the survey data. Ms. Considine stated that they had developed a frequently asked questions (FAQ) sheet that addressed these concerns and had maintained a good response rate. Mr. Smithson asked when the main study was scheduled to begin. Ms. Considine stated that it would begin January 2007. Mr. Smithson noted that veteran service organizations (VSOs), like the American Legion, needed three or four months of lead time to help promote the survey and encourage participation.

Dr. Meggs commented that nondeployed veterans don't equate with being nonexposed because organophosphate exposure is common, e.g. homes and offices are sprayed with pesticides. Ms. Considine stated that this information was asked about specifically on the questionnaire. Dr. Haley added that this was one of the questions they were going to explore, that is, what may have contributed to chronic multisymptom illness among the nondeployed. They planned to evaluate a sample of these syndromic veterans.

Chairman Binns opened the question period to members of the audience.

Mr. Kirt Love, an audience member and a Gulf War veteran, asked about the type of computer operating system (Oracle, etc.) that would be used. He expressed concerns about long-term access, either internet or intranet, for researchers and participants. He stated that there had been problems in the past because databases were not marriable because the objects were not recognizable. The question is how to simplify it so objects are recognizable on multiple platforms and multiple database systems. He added that researchers lacked the ability to invite participation from individuals through an intranet system, which would allow them to log-in and participate over time. How do we follow-up over a period of time, e.g., after six months or a year? Obviously the Internet is the easiest way. Mr. Love asked if they had an intranet location as well. Ms. Considine stated that Blaze was the platform being used. The information then would be put into a statistical analysis system (SAS) database. The information can be processed or manipulated from there. SAS databases are widely used across the industry. Ms. Considine stated that the study wasn't designed as a longitudinal study, but they will capture location information at the end of the survey to send participants their checks. Thus, if they need to go back and look at these veterans again, they will have this information. Mr. Love asked if the participants would have secure access to their own personal information, e.g., blood sample results or troop location information. Ms. Considine stated that she could not address the blood sample results because they were not conducting those tests. However, the information collected by RTI would not be available in an identifiable form.

The meeting recessed at 11:03 a.m. for a break.

The meeting reconvened at 11:17 a.m.

Dr. Haley introduced Drs. Spence and Briggs. Chairman Binns asked that questions regarding their presentations be held until the discussion period at the end of the day.

Brain Miner: Software for a new approach to analyzing brain imaging studies

Jeffrey Spence, PhD
University of Texas Southwestern School of Medicine

Dr. Spence gave an overview of the statistical benefits of his team's software, Brain Miner, when analyzing brain imaging data and explained how this software was being used to examine differences in resting blood flow in deep brain regions of ill Gulf War veterans and healthy control patients. (See Appendix A – Presentation 3.)

Neuroimaging Innovations to Detect Subtle Alterations in Brain Function

Richard W. Briggs, PhD
Director of Neuroimaging, Gulf War Illness and Chemical Agent Exposure Program
University of Texas Southwestern Medical Center

Dr. Briggs gave an overview of various neuroimaging techniques available to detect subtle alterations in brain function and the research being conducting at UT Southwestern to enhance the specificity and sensitivity of these techniques. (See Appendix A – Presentation 4.)

Dr. Haley noted that when UT Southwestern's Gulf War Illness and Chemical Agent Exposure Program was created, they entered into active collaborations with several other universities in the area, including the Engineering and Neuroscience Departments at the University of Texas-Dallas and the University of Texas-Arlington and the Statistics Department at Southern Methodist University.

Dr. Clauw asked how they envisioned using functional imaging to determine what was happening in Gulf War veterans. He stated that one had to be incredibly careful to have the appropriate control groups when using functional imaging because everything influences what is seen using these modalities. His group has shown that several techniques, including arterial skin labeling, functional magnetic resonance imaging (fMRI), etc., provide abnormal results in individuals with fibromyalgia, as well as those who have never left U.S. soil or been deployed. The techniques presented were wonderful and UT Southwestern has excellent researchers working to advance these methods, but Dr. Clauw noted that if the clinical research experiments were not designed appropriately, with the proper controls and accounting of confounding factors, one could interpret the results any way they wanted. Dr. Haley noted that Dr. Briggs had presented the background on the technology available, not a study. He agreed that the key is to develop the right groups of comparison subjects. This is why they are hoping to take advantage of findings from/ collaborations with the National Survey data, the brain imaging group and the animal research being done. At first, they will very carefully select small groups of normal and abnormal patients for pilot studies. Eventually, when they reach the biomarker phase, they will use cases and controls identified from the National Survey.

Dr. Clauw stated that it wasn't just cases and controls. In fibromyalgia studies conducted by his group, they have found that someone's pain level or mood at the time of a scan tremendously influences the results. This was especially true in areas with differential activation patterns, for example, in areas influenced by mood. Thus, the patient's level of depression, anxiety, and pain must be measured during every scan. Dr. Haley stated that Dr. Briggs was collaborating with another group to develop a neuropsychological core in order to address this very issue. He added that they were also looking to

identify groups of individuals who had relatively homogenous illnesses and that this is one of the hardest things to do. In order to identify these homogenous subgroups, they are putting much of their effort into examining clinical presentations and biomarkers. This will allow them to determine more meaningful averages within these subgroups and address some of the concerns raised by Dr. Clauw.

Dr. Jim O'Callaghan, a Committee member, commented that there were several end points suggested based upon this new technology. However, there doesn't appear to be a great deal of confidence yet as to what these changes from baseline may mean. Dr. Briggs agreed and stated that one of the challenges was determining the origin of these changes. One of the reasons they want to develop all of these different techniques is that they need all the data that they can get. For example, they need to determine whether loss of grey matter results in functional abnormality or just a loss in the amount of brain matter. Because there are overlapping etiologies and symptoms, data are needed to identify the various subgroups. Dr. Briggs said that he hadn't addressed this in his presentation, but it was part of their overall research plan. Dr. Haley stated that they hoped to do multiple tests on the same patients; perhaps even during the same session, so that they can look at what is happening in a patient's fMRI, electroencephalogram (EEG), and spectroscopy measurements. Then, by triangulation, they will learn more. Dr. Haley stated that their single photon emission computed tomography (SPECT) experiment findings, along with the ability to conduct pharmacological or cholinergic challenges in an hour, had a great influence on their approach.

Dr. Jack Melling, the Committee's consultant, noted that a complicating factor was that the patients in question were fifteen years out from whatever their initial injury had been. There is an assumption that there will have been compensation, repair, etc., and this is what would be seen in the neuroimages of these patients. Dr. Melling wondered if there would be value in looking at individuals who have been exposed to organophosphates more recently. Dr. Haley noted that Texas is a large state with an intense agricultural zone through the Rio Grande Valley. The individuals who live near these fields are often exposed to pesticides. There is a new epidemiologic study that will be looking at the people in the Rio Grande Valley and their symptomatolgies, with an eye to running similar tests.

Chairman Binns opened the floor to public comment.

Mr. Kirt Love suggested that some type of dietary trial be conducted. He then noted that fMRI had a delay in signals and a delay in interpretation, and thus was not in "real time." He stated that he hoped to have heard a presentation on the use of ultrasound to follow vasodilatation and blood flow patterns. Dr. Briggs stated that, even with fMRI or ultrasound, one of the difficulties is that these techniques measure several steps downstream from what they would really like to measure in some respects, i.e., brain function and activity. Thus, they are beginning to prioritize EEG testing. EEG is a method that has both time-resolution and the ability to tell something about brain activity. Dr. Briggs stated that Mr. Love's point was well-taken though and they may need to consider adding more "tools to their box" or techniques to supplement fMRI and EEG. Mr. Love stated that he mentioned this because people who have been sick for fifteen years don't exercise, so they have heart rate and blood flow irregularities. So individuals who are not exercising would be an excellent comparison group.

Chairman Binns thanked Dr. Briggs.

The meeting recessed at 12:35 p.m. for lunch.

The meeting reconvened at 1:33 p.m.

Dr. Haley commented that the afternoon presentations would focus on the preclinical aspects of UT Southwestern's research. Their goal is to develop a treatment. One of the ways to do this is to understand

how the disease works. Dr. Haley then introduced Dr. Christopher Sinton, Assistant Professor at UT Southwestern.

A rodent model of Gulf War illness: Development and validation

Christopher Sinton, PhD
Assistant Professor, University of Texas Southwestern School of Medicine

Dr. Sinton gave an overview of his research looking at whether low-dose, repeated exposure to acetylcholinesterase (AChE) inhibitor agents induce delayed, minimal brain dysfunction in rodents (rats and mice) and whether these animal models may provide insight into Gulf War illnesses. (See Appendix A – Presentation 5.)

Dr. Golomb, a Committee member, asked Dr. Sinton why he thought, other than that side effects can be reproduced, that the synergistic effect implicates dopamine involvement. Dr. Sinton stated that he was only speculating on these interesting results and what they might mean. They were not doing these tests to determine what these effects were, but it was interesting in a forum like this to note that a low-dose amphetamine given to mammals would also increase activity and nausea, but have no effect on other measures. He simply wanted to throw out this interesting corollary.

Dr. Carrolee Barlow, a Committee member, noted that chlorpyrifos and pyridostigmine bromide (PB) also inhibit butyrylcholinesterase and neuropathy target esterase (NTE). As she watched his slides, she noticed that his findings were similar to the findings from her group's work with NTE heterozygote animals. Given the fact that both of these drugs also affect additional esterases, it is important to note that pure acetylcholinesterase inhibitors on the market, like tacrine or donepezil, don't produce these side effects. They had looked at various things in rats, such as anxiety and depression measures, but never saw anything like Dr. Sinton was seeing here. They had also looked at amphetamines and many other things and she believed that it wouldn't pan out exactly like amphetamine once Dr. Sinton's group was able to look at it in a little bit more detail. She found their findings remarkable, but reiterated that the low-dose exposure results looked similar to the low-dose NTE work that she had done. Dr. Sinton commented that one of the purposes of the afternoon's presentation was to discuss what other possible mechanisms may be involved in creating this dysfunction. One needed to bear in mind that because these effects occurred so long after cholinesterase inhibition ended, it was unlikely that it was a cholinergic effect. Dr. Sinton noted that this was purely a hypothesis. Dr. Barlow agreed.

Dr. Meggs asked for clarification about the different dosages and percent inhibition found of whole brain AChE in rat and mice. Dr. Sinton discussed this and noted that they had found it more interesting to stay with the low doses.

Dr. Clauw asked Dr. Sinton to explain why an increase in the walking distance would be the direction one would expect to see if this was a Gulf War illness animal model. Dr. Clauw stated that when he saw Gulf War patients, many looked like individuals who needed amphetamines, not like individuals who were taking amphetamines. He stated that this was the exact opposite of what he would expect to see in an animal model that would represent Gulf War illness. Dr. Sinton responded that it comes down to how one interprets the test, as there are no obvious parallels. What one is looking at in the rodent is the drive to explore, which is an innate response in these animals. With increased activity, one is looking at whether the animal has an increased fear or inability to habituate to their environment. They don't know how this might translate into a human.

Dr. Clauw stated that this still appeared to be the opposite of what he would predict to happen in an animal model of Gulf War illness. Dr. Sinton noted that this was simply a screen to see if there was any change in the brain. They are simply saying at this stage that these animals' have had something changed in their brain following exposure to these chemicals. Not only did something change over a period of time, it seemed to increase over time. This is an indication of something like Gulf War illness, but doesn't mean it is Gulf War illness.

Mr. Hardie asked if it was possible that the animals might have had damage to their short term memory and are exploring more because they lack recall. Dr. Sinton replied that amphetamine use did affect memory and that could be an explanation.

Dr. Golomb commented that one of the relevant points was that chlorpyrifos and PB were two agents that Gulf veterans were known to been exposed to and that these agents lead to chronic changes in brain and cholinergic function. While it is known that there are big differences from species to species, e.g., difference in receptor types, we don't expect the same character change from species to species. The first question is: "Does it lead to persistent and delayed changes?" And the downstream question is: "How well do these changes map?" Dr. Sinton agreed.

Dr. Barlow commented that this was a crude screen so far with an impressive signal that opens the testing to a host of different conditions and agents. But as a screen, it can be used quickly to say "something is not right with these animals." It is an important test to have because many other assays are built off the same motivation that drives the open skills test. It is good to have this data. It allows one to think about other types of screens that won't be influenced by abnormalities due to locomotion, abnormal exploration, inability to remember things, etc. She added that they shouldn't overinterpret this as a particular phenotype, but it tells you that something is clearly abnormal in how the animal handles locomotion in a novel environment. But at the very beginning of the screen, one has to start layering other things to see what is really wrong with the animal. This is a model system, so it doesn't matter if it directly mimics the syndrome in humans. In fact, there are no models that directly mimic human systems. However, if the model reproduces some of the anatomical abnormalities or some aspect of behavior that can be monitored, one would have for the first time a model that could be used to test therapeutics. This is the value of this type of system.

Chairman Binns opened the discussion to very brief questions from the audience.

Mr. Kirt Love asked if Dr. Sinton's group had addressed glutamine receptors. Dr. Sinton replied that they had not.

Ms. Denise Nichols, an audience member and Gulf War veteran, commented that when these studies were being conducted, researchers should keep in mind the time period, as well as changes in Gulf War veterans and their behaviors. Dr. Sinton agreed and noted that they were interested in this model because they did see a progressive change over time in the animals.

Chairman Binns thanked Dr. Sinton.

Dr. Sinton introduced Dr. James Bibb, an Assistant Professor in the Department of Psychiatry at UT Southwestern.

Neuronal signal transduction in Gulf War Illness

James Bibb, PhD
Assistant Professor, University of Texas Southwestern School of Medicine

Dr. Bibb gave an overview of his research looking at the role of CDk5 in CNS function and how further research in this area might provide a biomarker, diagnostic tool, and treatment avenue for Gulf War illness. (See Appendix A – Presentation 6.)

Dr. Golomb and Dr. Bibb discussed how a mechanism involving excess cholinergic signaling following organophosphate and/or nerve agent exposure could lead to increased glutamatergic activity.

Chairman Binns thanked Dr. Bibb.

Dr. Sinton introduced Dr. George DeMartino and Dr. Philip Thomas, who are both professors in the Department of Physiology at UT Southwestern.

Organophosphates and the structure and function of the ubiquitin-proteasome system

George DeMartino, PhD, Professor
Philip J. Thomas, PhD, Professor
University of Texas Southwestern School of Medicine

Dr. DeMartino gave an overview of the ubiquitin-proteasome system and discussed how inhibition of proteasome activity can lead to protein aggregates, producing several neurological diseases. (See Appendix A – Presentation 7a.)

Dr. Thomas discussed protein misfolding and accumulation of α-synuclein fragments that are not degraded by protesomes. (See Appendix A – Presentation 7b.)

Chairman Binns thanked Drs. DeMartino and Thomas.

Dr. Sinton introduced Dr. Ilya Bezprozvanny, an associate professor in the Department of Physiology at UT Southwestern.

Neuronal cell culture model for the study of Gulf War illness

Ilya Bezprozvanny, PhD
Associate Professor, University of Texas Southwestern School of Medicine

Dr. Bezprozvanny discussed parallels between Gulf War illnesses and Huntington's disease and how Huntington's disease research could inform the development and design of Gulf War illnesses research and treatments. (See Appendix A – Presentation 8.)

Dr. Meggs noted Dr. Bezprozvanny's comment that Huntington's disease resembled Dr. Haley's Syndrome 2 patients early on, except for the disease progression. Progression curves, reflecting disease severity, are very flat for a period of time and then they take off. He wondered if it was possible that we haven't yet reached the "take-off" period in Gulf War patients. Dr. Bezprozvanny stated that the difference was that Huntington's disease was genetic and present since birth, while Gulf War veterans were exposed for a short time. The fundamental difference is that a toxic protein is always present in Huntington's disease, while the Gulf War exposures were limited and resulted in less damage. Dr.

Bezprozvanny noted that Co-Q10 wasn't a cure for Huntington's disease, but rather slowed its progression. Dr. Meggs stated that it was known that individuals who have been acutely poisoned progressed over a period of months to this profound encephalopathy. He knew of one case where the full extent of the disability didn't occur until 9 months after the exposure.

Dr. Golomb commented that, when she served as scientific director of the Committee, she had presented a briefing which postulated that Gulf War illness was a mitochondrial disorder and that Co-Q10 was a potential treatment. Dr. Haley stated that, after talking with Dr. Bezprozvanny about this hypothesis, he knew that Dr. Golomb would be quite interested. Chairman Binns noted that the RFA would provide Dr. Golomb and others with resources to test this hypothesis in Gulf War veterans.

Mr. Hardie asked Dr. Bezprozvanny whether he was looking at immune system dysfunction too. Dr. Bezprozvanny said that another UT Southwestern researcher was looking at this question. Mr. Hardie stated that he was curious because, given his own experience, he wasn't so sure that there wasn't a progression in Gulf War illness. Dr. Bezprozvanny clarified that there was a progression, but it wasn't as fast as Huntington's disease.

Chairman Binns open the discussion to members of the audience.

Dr. Ruth McGill, an audience member and a physician, commented that she had been taking Co-Q10 since 1994. She stated that she had been required to supplement other nutrients while taking Co-Q10. There seemed to be a gradient or prioritization of nutrients and Co-Q10 should be the last resort. A patient can be over stimulated by Co-Q10, which leads to vitamin deficiency. She believed that Gulf War veterans should have received this treatment immediately upon developing symptoms. It might have prevented the worsening of the symptoms. She stated that she had referred two patients to one of the Co-Q10 international experts. She discussed these patients' conditions, one of whom had amyotrophic lateral sclerosis (ALS). She stated that it was a promising treatment, but more research was needed. She thanked Dr. Bezprozvanny for his presentation. Dr. Bezprozvanny commented that if mitochondrial damage had occurred, Co-Q10 wouldn't cure the individual. He made a comparison to the use of better quality gas in an old car. Drs. Bezprozvanny and Golomb discussed the rationale for the hypothesis that Gulf War illness was a mitochondrial disease.

Mr. Kirt Love asked if there was evidence of mitochondrial regeneration. Dr. Bezprozvanny stated that this could be studied in animal models via mitochondrial imaging, but he didn't think anybody had done this yet. He stated that he also didn't think this could be done in human subjects. Dr. Golomb commented on the mitochondrial protection provided by Co-Q10.

Ms. Denise Nichols commented that that she took Co-Q10. She suggested that if there were things that might be helpful, it would be good if this information was passed along to doctors and veterans. Dr. Mary Nettleman agreed with this sentiment, but thought clinical trials were needed to make sure recommendations were for things that work. She suggested that the DoD RFA was a possible avenue for this type of study and noted that it was a testable hypothesis.

Chairman Binns thanked Dr. Bezprozvanny.

Dr. Jack Melling asked if there were other compounds that might breathe new life into damaged mitochondria. If one was considering clinical trials, it would be better to have more than one treatment option to test. This is often a powerful way to run the study. Dr. Haley stated that there were several ideas about candidate treatments. However, what the field currently needed to do was use animal models to test the most likely targets of organophosphate damage, three of which were presented that afternoon.

When these targets are identified, they could start testing these other possibilities. He added that it would also be reasonable to start testing things they already knew about.

Dr. Golomb commented that Co-Q10 was the most commonly used antioxidant clinical treatment, but there were other antioxidant cocktails. She discussed some problems with these other antioxidants, which included becoming prooxidant at high doses.

Dr. McGill discussed the work of Dr. Douglas Wallace on this subject. She noted that damaged mitochondria will replicate faster than healthy mitochondria, which makes the problem even worse.

The meeting recessed at 3:32 p.m. for a break.

The meeting reconvened at 3:46 p.m.

Approaches for assessing treatments for Gulf War Illnesses: the UT Southwestern experience

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

Dr. Haley discussed various approaches that had been previously used to test treatments for Gulf War illnesses and potential options for future treatment trials. (See Appendix A – Presentation 9.)

During the discussion of previous clinical treatment trials in Gulf War veterans, Dr. Clauw noted that he had been a principal investigator on the cognitive behavioral study. This study was done because the investigators thought it would work. It was also done as an effectiveness trial for incorporation into VA practice. He stated that the primary end point was actually positive, but he would agree that the effects were very modest. The other treatment trial involved doxycycline. This trial was done to either prove or disprove a mechanistic hypothesis. These trials were quite different. Dr. Golomb commented that it was worth noting that the average change in functional status for both treatments was a 1% improvement.

During the discussion of UT Southwestern's treatment pilot study findings, Mr. Hardie inquired about the improvement while taking lorazepam. Dr. Haley indicated that was there was slight improvement. He indicated that if this study was repeated, the focus might be placed on studying lorazepam and pindolol. Dr. Golomb commented that if the study was done with a benzodiazepine, such as lorazepam, it was important that the trial be for a long duration.

Dr. Steele inquired about the extent of controversy surrounding n-of-1 trials. Dr. Haley stated that n-of-1 trials were extremely controversial. When this study was proposed in 1997-1998, there was an intense negative response. The Perot Foundation ultimately funded the study, but when he had initially proposed the idea, he had been told that only formal, randomized, multi-center experiments could provide researchers with meaningful information about drugs and that had clearly been the message over the past ten years. Dr. Haley hoped that this would change, because experimentation to identify drugs as candidates for more formal trials was needed.

Dr. Steele stated that she had the impression that different panels of the National Institutes of Health (NIH) and U.S. Food and Drug Administration (FDA) have looked at the use of n-of-1 trials. She asked Dr. Haley if these panels had set forth guidelines on how to interpret n-of-1 trials. Dr. Haley noted that this particular study wasn't really an n-of-1 trial, but rather a cross-over trial with fourteen patients. They had started out designing an n-of-1 trial, but migrated from there to a cross-over trial. They could have analyzed it a little bit more creatively, but they wanted to be careful about torturing the data.

Dr. Golomb agreed that it seemed to be a small cross-over study. She stated that one thing researchers could do to improve the power of their studies was to repeat a test a number of times at each stage. She noted that one n-of-1-trial had been published looking at adverse effects of statins on mitochondrial function. There is precedent for small studies, especially those with subjective outcomes. Dr. Haley noted that they had tested the effects of five drugs in fourteen bonafide cases. If they had found a large effect, it would have led them in a direction for further study. Two drugs showed promise, but Dr. Haley acknowledged that this could be due to sampling error. He indicated that more investigation was needed. He noted that the study cost $500,000 because the study evolved while they did it. He stated that it could be franchised for less once the process was worked out. Whether this was worthwhile was a philosophical question that needed to be addressed.

Dr. Melling asked whether this approach had been used successfully with respect to other conditions and drugs. And if so, was a particular drug identified that then went into general use? Dr. Meggs responded that he thought this was an intelligent approach. If you have a magic bullet, e.g., insulin for Type 1 diabetes, you only need one patient to determine if it is a great treatment. Dr. Meggs stated that it appeared that none of the drugs used in the study were magic bullets. Dr. Haley agreed that none of these drugs, in the dosages used, were a magic bullet. He believed that the study needed to be extended. The patients needed to be brought into the clinic and have their medication dosages increased until there were signs of toxicity or benefit.

Dr. Golomb commented that, in the case of pindolol, there were interesting problems where the autonomic arousal itself can promote symptoms. However, there were a couple of mechanisms for what we already knew about ill Gulf War veterans that could create plausibility around this approach.

Dr. Clauw stated that n-of-1 trials were reasonably well-accepted, but generally were never published. They are usually used in a different setting, i.e., to determine what subset of the population is benefited by a particular drug, out of multiple drug options. He stated that he would be careful about using an n-of-1 trial for the reason being articulated today because there is no blockbuster drug for Gulf War illness. Unless there is a new chemical entity, clinicians who already treat Gulf War veterans and individuals with fibromyalgia have already thrown everything at this. When they see something that anecdotally works, clinicians take note of it. He stated that it could be problematic to evaluate Co-Q10 or something else with a reasonable basis for efficacy in an n-of-1 trial because it will be underpowered. It is unlikely that one would be able to see the efficacy. Dr. Clauw indicated that he would only use a n-of-1 trial in the setting of Gulf War illness to: (1) assess subsets of Gulf War veterans with different types of drugs, or (2) examine a couple of really bizarre and/or expensive drugs that haven't been tested in Gulf War veterans to see if one gives a blockbuster signal. However, he would not use this approach with the drugs that they have a reasonable expectation that they will work. Dr. Golomb said that she generally agreed, but didn't think the approach was completely unreasonable as a way to initially explore a treatment.

Dr. Barlow noted Dr. Clauw's earlier comment that it was clear that there was a fraction of ill Gulf War veterans that seemed to have something related to glial hyperactivity, e.g., those with ALS. These veterans clearly have something unique. However, the global population of Gulf War veterans may not fall into this category. There is another idea, now, around a mechanism of organophosphate toxicity, which is very appealing and compelling, that might generate another set of problems that might not fall into exactly the same category. She noted that Dr. Haley had identified three syndromes. She wondered if there was a way to utilize and adapt this approach in order to: (1) characterize veterans' symptomatology, (2) provide better subgrouping of the patients, and (3) determine what symptoms if any a particular drug might affect.

Mr. Hardie noted Dr. Haley's concern about recruiting enough Gulf War veterans for studies. He said that he was a participant in the doxycycline treatment trial, and that the local VA had been effective in getting the word out to veterans in the Milwaukee area. They utilized newspaper and radio, putting him out as a "poster child" with this illness and inviting other veterans to participate in the study. The study coordinator had reported that this had been extremely effective and they had a larger than expected group of participants. He was more than happy to share the specifics with Dr. Haley or anyone looking at doing something like this. The key thing is to get the word out.

Dr. McGill discussed her own experience as an n-of-1 success story. She consulted the best experts in certain subspecialities and brought this information back to her primary doctor. She thought Dr. Haley's categories were good and didn't question his n-of-1 design. However, she would caution that juggling all of these drugs was really dicey. She did not recommend this to patients who were not physicians or nurses. She also wouldn't recommend it without basing the approach around different treatment's healing effects, as opposed to symptom-related properties. She is on a heavy-duty nutritional regimen, which works well for her. She pointed out that her timeline as an n-of-1 success story covered a period of 25 years. She added these drugs one at a time, with years in between, and often would not get an immediate effect, which was discouraging. She hoped that Dr. Haley could make this approach systematic.

Chairman Binns inquired as to the specifics of Dr. McGill's nutritional regimen, which included intake of Vitamin B12. Dr. McGill discussed the dosage and schedule she follows with respect to Vitamin B12 intake. She discussed problems experienced by patients with mystery chronic illnesses, such as having to continually maintain treatments once they are begun. Several things need to be considered when the nervous system, which affects every body system, is involved. She believed that n-of-1 trials were an approach that would work, but one had to take the complexities and complications into consideration. She stated that more was needed than a blinded psychologist to follow these patients.

Dr. Clauw commented that Dr. McGill had brought up good points with respect to the patient burden of n-of-1 trials. When VA did trials across the country, no site was able to recruit more than 20-25 patients. This is why they had 20-25 sites in the trials. This was also 10 years ago when theoretically Gulf War veterans would have been more likely to participate. This is going to be an issue whenever a researcher goes to recruit 20-25 individuals at a single site. It is an issue for every clinical trial done. Dr. Steele stated that she had heard from several investigators over the years that they had had trouble recruiting Gulf veterans, especially healthy controls. However, this was the opposite of her experience while conducting her Kansas study. She stated that the veterans were very happy to participate, resulting in a very high response rate. She thought part of it may have been attributed to the fact that the study wasn't a VA study, but rather through the State of Kansas and private research institutes. Dr. Clauw stated that if one did clinical trials properly, an individual would come in once a week. The burden of a clinical trial was considerably greater than the burden of a mechanistic study where individuals are asked to come in a single time for one or two hours. Dr. Steele noted that she had referred veterans to Dr. Clauw when she received calls from veterans who wanted to be in trials. She indicated that the veterans seemed to express more interest when they heard that he was at the University of Michigan versus a VA facility.

Mr. Mike Griffin, an audience member and a veteran stationed in the Gulf in 1988 and 1993, spoke to the Committee about his experiences in the Gulf and resulting health conditions. He stated that when one was talking about Persian Gulf veterans there were two groups to consider: (1) those that served up to and through Desert Shield; and (2) those who served after February 27, 1991. He stated that there was probably a whole group of veterans that would never come into the VA. He expressed dismay that there was a lack of information as to: (1) how many Gulf War veterans had died, and (2) how many suffered from motor neuron disorders that could not be categorized. He discussed the trials and tribulations that he has undergone to find treatment, taking the journey one step at a time. He stated that he, along with many

other veterans, was "ticked off" at the VA. He stated that eligibility for clinical trials generally includes specific dates when a veteran served in the Gulf. If one didn't fall into the range, the veteran is not eligible for the trial. He discussed his efforts to lobby for legislation at the federal and state (Oklahoma) government levels. He stated that veterans who served in the Gulf from 1982 forward should be part of the studies being conducted. He noted that there would be problems recruiting healthy controls from this group because many of these veterans have served in the military and/or as civilian contractors in several conflicts, including the current deployment. This is also compounded by multiple deployments over time.

Chairman Binns thanked Mr. Griffin for his comments.

Dr. Meggs commented that the Committee had previously discussed how deployed and nondeployed individuals were not necessarily the same as exposed and nonexposed individuals. He stated that it would be very interesting to know what Mr. Griffin had been exposed to while stationed in Riyadh. Mr. Griffin stated that the winds blew from the Northwest in this area, bringing lots of sand coated with toxins. He noted that Iraq first released chemical weapons against Iran in 1982. He stated that U.S. forces were wearing chemical gear in 1983 and 1984. When he arrived in 1988, he was told about this. Dr. Meggs stated that it sounded as if Mr. Griffin had been much more ill at one time. He asked Mr. Griffin if he could identify the treatments that had helped him get to the point where he could participate in the day's meeting. Mr. Griffin stated that it he wouldn't call it improvement, but rather keeping the symptoms in remission. He discussed his diet, including avoidance techniques, among other things. He stated that he was now service-connected for multiple sclerosis (MS).

Chairman Binns asked if anyone knew of studies looking at potential exposures during the Iran/Iraq War, and additional questions were raised in the discussion that followed about the health of the civilian populations in these countries. Dr. Steele stated that there was limited information about this population. She noted that there was a descriptive report prepared by a British clinician relating to her observations in Halabja following the use of chemical weapons on the local Kurdish population. She also noted that there were several studies that examined the effects of mustard gas on Iranians who were exposed during the war. The studies looked at various effects, including neurological, respiratory, dermal, etc. There appear to be well-documented chronic sequelae associated with mustard gas exposure.

In response to Chairman Binns' question about research on local Iran/Iraq populations, Dr. McGill noted Dr. András Korényi-Both's hypothesis regarding Al Eskan disease. She stated that she had received a letter from a Kuwaiti physician asking for help with the increase in chronic fatigue patients he was seeing. She noted that there were also several undocumented reports of an increased rate of leukemia among Iraqi children.

Mr. Kirt Love stated that Gulf War veterans were twice as likely to have seborrheic dermatitis and that this condition was also associated with mustard gas exposure.

Chairman Binns asked that the rest of the discussion be among Committee members about UT Southwestern's treatment and research program. He noted that there would be additional time after that for public comment.

Dr. Nettleman asked if anyone knew why Dr. Han Kang's most recent study findings had not been published yet. She felt that it was important to make sure there was more published on this issue. Dr. Haley stated that he did not know why these findings hadn't been published. He noted that Dr. Kang had heeded the Committee's recommendations and modified his study to include questions about treatments. The preliminary findings of this study were reported to the Committee a year ago. Dr. Haley stated that the Committee may need to request a new progress report. He expressed his belief that Dr. Kang was one

of the great heroes in this area of research. Dr. Kang is in one of the most difficult operating environments in the country and has still been very productive in this area of research. Dr. Haley suspected that publication of the findings was on Dr. Kang's agenda, but it was a matter of moving it to the top of his list. Dr. Steele stated that Dr. Kang would be presenting some findings from the treatment data at the International Chronic Fatigue Syndrome conference in January 2007.

Dr. Floyd Bloom commented that the afternoon presentations demonstrated that Dr. Haley had assembled a group of high quality collaborators. He wondered, however, if they had a more straightforward analysis of the model that they would be pursuing. He suggested that they may think about doing a genomic comparison of the parts of the brain that have been shown to be affected at particular periods following exposures. The gene chips available today are much better than they were five years ago and are pretty consistent, at least in rodents. He asked if this type of research was being considered. Dr. Haley stated that it was on the "drawing board" and was considered an important priority.

Dr. Steele asked Dr. Haley, with respect to the epidemiologic portions of the National Survey, if they would be working to optimize the case definitions and identify symptom patterns and subsystem patterns that distinguish the deployed and nondeployed veterans, making sure to keep out individuals with other diagnosed conditions. This is a golden opportunity to improve on what everyone has tried to do, that is, identify the most optimal case definition. Dr. Haley stated that the first step would be to determine the prevalence of these existing case definitions in their original incarnations, because these are hypothesis tests that have been done over and over. They want to confirm these hypotheses. Once they do this, they will take a random half of the sample and try to reengineer what is the best case definition and then try to replicate it in the other half. Dr. Steele asked whether they would use this new case definition or pre-existing case definition(s) for the follow-up clinical studies. Dr. Haley stated that they hoped to come up with a better case definition or several variant definitions. However, it was possible that they would find that they should go with the original definitions. Dr. Steele noted that the Fukuda case definition was based on Air Force veterans, while Dr. Haley's case definition was based on a group of Navy veterans. However, it seemed that Army and Marine veterans were most affected. Dr. Haley stated they may reject their previous findings or determine that it was overly modeled on that particular group, so it may not replicate the same. However, if it doesn't replicate, they will have a large enough "n" to explore half the sample and replicate in the other half. They will not move ahead with the clinical sample until they have solved this problem. Dr. Steele commented that exposure profiles for different military branches were distinct. Dr. Haley agreed.

Dr. O'Callaghan commented that the Committee had seen several nice preclinical models in the day's presentations. He thought that they should move ahead and do as much phenotyping with as many multiple end points and classes of evaluations as possible. He noted that proteomics and genomics processes could now be done very rapidly and inexpensively in these animal models.

Dr. Clauw stated that the Committee should consider whether it should make a recommendation as to which case definition should be used. Otherwise, everyone will use something different and it will be difficult to determine what worked and didn't work in treatment trials. He stated that he didn't know what would be the "right" case definition and that it wouldn't be simple to address. However, it would make the aggregate research conducted under the DoD RFA more meaningful. Dr. Steele stated that the Committee had discussed doing this previously. Some Committee members were opposed to even suggesting that there be a case definition, while others believed that there needed to be something to start with. The only consensus that could be reached at that time was that if a case definition was used, it had to be described clearly. She stated that, in order to identify the best case definition, the Committee would have to do some analyses that compare the various case definitions ability to distinguish groups. There are ways to do this, but no one has done it in a systematic way. She thought most people would probably

use the Fukuda case definition, noting Dr. Haley's definition required an extensive questionnaire. She stated that a few researchers had used the Kansas definition and that it was reasonably easy to use. Even though she had worked a lot with the case definition issue, it would be hard for her to say what specific components should be used in an "optimal" definition. Dr. Clauw stated that, based upon the data presented by Dr. Haley, he would use Dr. Steele's Kansas definition. One of the things learned from previous Gulf War studies was that the Fukuda definition was too diffuse; many who met these criteria weren't sick enough. This is why the PCS score had to be superimposed to make things better. Without doing all these macerations, the Kansas definition obtained approximately the right percentage of people that we intuitively think were affected. Dr. Clauw stated that it never seemed right that the Fukuda definition found 15% of the general population and 45% Gulf War veterans had this problem. If this is what we use as a basis for treatment trials, it might cause some problems. Dr. Steele noted that some studies have found the prevalence to be 60% in Gulf War veterans vs. 35% in nondeployed veterans using the Fukuda case definition.

Chairman Binns commented that Dr. Clauw's recommendation was a good one. However, given the amount of time before the letters of intent were due under the DoD RFA, it wasn't likely that this recommendation could be publicized. Dr. Clauw indicated that he would use the Kansas definition. Dr. Steele stated that, even though she hadn't published more specifics yet, the Kansas definition was consistently more specific than the Fukuda one. They both generally identified associations and exposure effects in the same direction, but the Kansas case definition consistently provided higher odds ratios for those effects.

Dr. Meggs stated that the Committee had heard many times how a subset of Gulf War veterans get better when they quit using irritant household products and fragrances or changed their diet. This is a hard thing to evaluate in a blind study. If one wanted to do a small pilot study to evaluate the improvement in a subset of Gulf War veterans in an environmental control unit, they would need subjective markers to determine improvement. Dr. Meggs pondered what type of design would be used in this type of study. Dr. Steele stated that there was a small amount of literature on doing clinical trials of therapies that don't lend themselves to blinding, e.g., chiropractic, massage, etc. The gold standard is the randomized, double-blind, placebo-controlled, trial. However, if this is not possible, the question is what is second best. All of the literature that she has read says that, at minimum, randomization is the component that is not expendable.

Before ending the day's discussion, Chairman Binns noted that Dr. Jau-Shyong Hong, who spoke at the Committee's August 2006 meeting, had referenced a website that discussed low dose naltrexone treatment. Chairman Binns provided the Committee with the full URL: www.lowdosenaltrexone.org. He noted that a clinical trial of naltrexone for Crohn's disease had been done at Penn State Hershey Medical Center. It involved about 40 people. They found many of the individuals got better. As a result, NIH has given the medical center $500,000 to do a larger study. Chairman Binns stated that n-of-1 and $10 million, multi-center trials were the extremes, but there seemed to be a lot of accepted ground in the middle. He asked Dr. Steele to summarize some of those research approaches. Dr. Steele stated that many present were probably familiar with the "hierarchy of evidence" concept. She said that the Committee had talked over the years about collecting systematic information on treatment outcomes and using this information to determine candidate treatments for clinical trials. There are groups at NIH, including the National Cancer Institute (NCI), that have been faced with evaluating unconventional therapies for which there is little evidence and no animal models. One of the techniques used at NCI is the "best case series". They have established guidelines for clinicians to report their very best treatment outcomes. There is another protocol developed at NIH's Office of Complementary and Alternative Medicine called the "prospective outcomes monitoring evaluation system" or POMES. This is clinically-

based outcomes research. There can be an element of randomization, but it is often used in practices where one type of treatment is used routinely. She discussed how this type of study would be designed.

Chairman Binns thanked everyone for the day's discussion.

Public Comment – Day 1

As several individuals had signed the public comment sign-in sheet, Chairman Binns clarified who was still present and wished to make comments.

Mr. Griffin spoke to and thanked the Committee. This was his first time to attend a Committee meeting, but he had attended town hall meetings held by DoD and the Presidential Advisory Committee. He indicated that he read all the information available on this subject. He stated his belief that troops were exposed to weapons of mass destruction in the Gulf. He expressed frustration with the multiple tests and signed waivers that he had experienced to determine what was wrong with him. He discussed problems faced by other Gulf veterans in obtaining treatment and disability payments. He stated that Gulf War illnesses were unique and couldn't be compared with other known diseases. He stated that the thinking in this area needed to be revamped.

Ms. Nichols spoke to and thanked the Committee. She provided a summary of a written statement from Mr. Carl Musgrove, a retired British Army officer and Gulf War veteran. He suffers from Parkinson's disease. He expressed concern about the British troops' use of PB during the 2003 invasion of Iraq, despite all of the evidence suggesting that PB might be responsible for 1991 Gulf War veterans' illnesses. He indicated that several of the U.K. veterans from the 2003 invasion were exhibiting illnesses similar to those of 1991 Gulf War veterans. He noted that US troops didn't use PB in 2003. Ms. Nichols expressed her own concern for the current troops. She stated that the troops were having symptoms that were not connected to their wounds. Clues were missing as to the cause of their symptoms. She stated that several were dying natural deaths, just as Gulf War veterans had. She asked that the DoD leadership be asked to maintain a record of these natural deaths. She stated when the surveys and questionnaire data was collected, they also need to look at the data from the 22,000 Comprehensive Clinical Evaluation Program (CCEP) participants. There was a lot of data that needed to be included in the new research efforts. The CCEP covered the entire country. She stated that there also needed to be analyses of the Gulf War veterans' audiology and visual tests. This research may give us more answers.

Mr. Love spoke to the Committee. He noted that only 4% of the CCEP participants made it to Phase II. He stated that he had intended to present a PowerPoint presentation, but unfortunately had forgotten to bring it with him. Mr. Love discussed his personal health issues since the Gulf War and the steps he had undergone to find treatment. Based on his own experiences, he suggested that more dietary trials be conducted to find treatments for Gulf War veterans. This could be done in combination with the brain imaging studies being proposed. He stated that one of the issues with databases was that gait disturbances, which a lot of Gulf War veterans have, slip through the system. It is a very specific and visual observation that doesn't show up in the database. He also suggested doing: (1) spectroscopy and chemical analyses of the fatty tissue of Gulf War veterans to determine what is being retained in this tissue; and (2) bacterial cultures of Gulf War veterans. He noted that current troops were returning from Iraq with drug-resistant *Acinetobacter baumannii*. He stated that this particular strain of bacterium was present in Iraq and Iran back in 1988. The strain developed because veterinary drugs were being used to treat Iraqi people. Thus, it was endemic to the area during the 1991 Gulf War. As far as the seborrheic dermatitis, Mr. Love stated that this was related to mustard gas exposure. If tissue biopsies or skin scrapings of the areas affected by seborrheic dermatitis were conducted, we might find something. He

stated that most Gulf War illnesses were taken for granted and the subtle clues were being missed. As a Dallas Gulf War clinic probably wouldn't be established soon, he noted that there was a relatively new naval clinic at Corpus Christi, i.e., Ingleside, that could be converted into use as a research clinic. Dr. Steele asked Mr. Love about the source reporting an increase in seborrheic dermatitis. Mr. Love stated that it had been reported in a UK Gulf War veteran report. He indicated that he would forward this information to her.

Ms. Connie Gonzales, an audience member and a Gulf War veteran, spoke to the Committee. She discussed her health issues, as well as the problems and side effects she experienced with several of the treatments that she had received. She asked that Gulf War veterans not be turned away when they go to the VA. Her symptoms and pain were real. She expressed frustration with the amount of time it takes before one sees a VA specialist. She stated that she had medical bills, amounting to a several thousands of dollars, that needed to be paid because she had to go to the emergency room. She asked why she hadn't been given a physical before going to the Gulf War. If she had received the physical, she would not have gone to war. She was pregnant. If she hadn't gone, she and her son would not have the multiple disabilities that they have now. She stated that if the Gulf War veterans couldn't be cared for, the current soldiers could not be cared for either. She had thought the war was over when she got home, but it wasn't. She had been seeing physicians for fifteen years and hadn't found relief or a cure. She asked the Committee where she could go for the help.

Chairman Binns stated that this was sobering and an appropriate way to conclude the day's meeting. He stated that this was why the programs being proposed at this meeting and through the DoD RFA were so important.

The meeting recessed at 6:11 p.m. for the day.

Day 2

The meeting reconvened on Tuesday, November 7, 2006, at 8:35 a.m. at the Dallas/Fort Worth Airport Marriott North, 8440 Freeport Parkway, Irving, TX. Dr. Golomb was not present for the second day of the meeting.

Chairman Binns thanked Dr. Steele and the Committee staff, Barbara LaClair and Laura Palmer, for coordinating the logistics of the meeting.

Update: Highlights of Recently Published Research Relevant to the Health of Gulf War Veterans

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

Dr. Steele gave an overview of recently published research findings relating to Gulf War veterans' illnesses. (See Appendix A – Presentation 10.)

During the discussion of the Golier study and its finding that enhanced cortisol suppression in response to dexamethasone is associated with Gulf War deployment, Dr. Clauw commented that these findings were similar to findings in fibromyalgia patients. He added that the Golier study was designed to only look at deployed individuals with symptoms. So, the researchers couldn't disassociate deployment effects from veterans' symptoms. Dr. Steele noted that Dr. Golier had looked at symptoms in the nondeployed veterans as well. Dr. Clauw commented that the findings were the same type of thing seen in

fibromyalgia patients. Levels of corticotropin-releasing hormone (CRH) in the spinal fluid and hypothalamic-pituitary-adrenal axis (HPA) function are related to pain symptoms, regardless of whether the individual has posttraumatic stress disorder (PTSD). They are related to the amount of musculoskeletal pain people have at the time of test. It is a driving force behind the HPA findings, irrespective of anything else. HPA function is also affected by whether the individual had early childhood sexual or physical abuse. For individuals with this spectrum of symptoms, musculoskeletal pain levels are the driver behind what is seen at various levels of HPA function.

Dr. Steele commented that in Dr. Golier's study, this association was not found in the nondeployed. Dr. Clauw stated that the nondeployed were nonsymptomatic and didn't have significant musculoskeletal pain that would drive their HPA function. He noted again that this was what was seen in fibromyalgia, though it was not expected. They had thought the HPA findings were causing the symptoms of fibromyalgia and chronic fatigue syndrome, but it is the opposite. It is more likely the symptoms are causing the HPA findings. Dr. Haley asked how they were able to determine which one was driving the other. Dr. Clauw stated that there were other fibromyalgia/chronic widespread pain/post-motor vehicle collision studies that suggest baseline HPA findings prior to symptoms are a diathesis, predicting the subsequent development of symptoms. The current thinking in fibromyalgia now is that a healthy, asymptomatic individual is at higher risk of developing pain, fatigue, and other symptoms if they are at either end of the baseline bell-shape curve with respect to HPA measures, either hypo- or hyper-, and then subjected to biological stress. When these individuals are examined five or ten years later, the major correlate is that the pain levels are related to the HPA findings. Fatigue and other symptoms do not correlate at all. This is why they think it is a cause and not an association. Dr. Steele commented that she considered these findings very interesting, that people who deployed, whether or not they have PTSD, have differences in HPA function from people who did not deploy. The fact that this was independent of PTSD added an unexpected twist, as did the connection with using PB.

Following the presentation, Ms. Nichols inquired about Dr. Roy, the principal investigator on the study presented that looked at the combined effects of PB, DEET, permethrin and stress. She indicated that ill Gulf War veterans had not received the best care from him. Dr. Steele asked if Ms. Nichols was sure that this investigator was the same person. She stated that she had seen more than one Gulf War researcher with the same last name.

Dr. Steele noted that the Committee's website contained links to the PubMed abstracts of journal articles distributed to Committee members.

The Veterans Affairs Biorepository Trust Gulf War Brain Bank

Louis Fiore, MD
Co-Director, VA Boston MAVERIC

Dr. Fiore gave an overview of the process involved and issues surrounding the establishment of VA's Gulf War brain bank, along with an update on the progress that had been made. (See Appendix – Presentation 11a.)

Following Dr. Fiore's presentation, Dr. Meggs asked if they were collecting both brain and spinal cord specimens. Dr. Fiore indicated that they would do this for patients with ALS and other neurodegenerative diseases. In other cases, it might not be technically possible to collect spinal cord tissue. Dr. Meggs suggested that they might utilize a strategy to take two vertebrae and some spinal cord tissue so that researchers would have the nerve root for future study. Dr. Fiore stated that he would have to defer to Dr. Anil Prasad as to whether this was easy to do. Dr. Haley stated that, from his experience, it wasn't

difficult to obtain the first couple of branches of the spinal cord without disturbing vertebrae. Dr. Prasad agreed that this could be done and that their intent was to collect spinal cord samples.

Dr. Meggs asked Dr. Clauw for his opinion on what tissues should be banked for multisymptom illness research. Dr. Clauw stated that primary tissue would be brain. This is where the resources should be focused. He agreed that spinal cord would also be nice to have. However, if it cost twice as much, it would be better to have twice the number of brains.

Chairman Binns asked for clarification on the number of Gulf War veterans in the ALS registry. He understood that there were 1000 veterans in the registry, with 100 being Gulf War veterans. Dr. Fiore stated that this was correct but was not sure about what percentage of these Gulf War veterans had deployed. Dr. Steele stated that she had been informed by Dr. Oddone's team that there were about 50 ALS Gulf War cases. Dr. Fiore stated that to have 50 brains of ALS patients with the unique exposures of the Gulf War was invaluable. Animal models are almost all that researchers have now, which are inadequate but still very much needed.

Chairman Binns asked if Dr. Fiore knew when they would reach the second phase of the project that would include Gulf War veterans who didn't have ALS. Dr. Fiore stated that they wanted to start filling the tissue bank first. He would like to see about a dozen brains from ALS patients. Then they will begin speaking with VA Central Office about what was feasible and what was not. He didn't think that a large amount of resources would be needed. Their initial proposal was to do the tissue bank as presented. However, he thought that the collection of additional brains, as opposed to other tissues, would be under the purview of the initial submission. He anticipated that they would be thinking and planning the additional collection over the next six months. They will probably start doing something before the end of 2007.

Dr. Steele noted that there were so few Gulf War veterans in the overall ALS registry and asked whether initial efforts would be focused on enrolling Gulf War veterans into the brain bank. Dr. Fiore indicated that they would focus on Gulf War-era veterans and then additional controls beyond that. Dr. Steele said that she understood that they hoped to target individuals who were in imminent danger of dying. She noted that there were other concerns for Gulf War veterans, such as non-ALS neurological diseases (Parkinson's, MS, etc.). She asked if they intended to do an information campaign so that anyone with Gulf War illnesses or neurological problems associated with Gulf War service was aware of the bank. These individuals could begin providing their clinical information, blood and other tissue samples. This would then make the bank a comprehensive Gulf War resource. Dr. Fiore stated that they had discussions about doing this. It spoke to the question of how long it would take researchers to get to these veterans. He stated that they needed to get the first part running before more was contemplated. He indicated, however, that he understood why the Committee was pushing for more.

Dr. Steele asked who would be able to access and use the tissues collected. Dr. Fiore stated that the tissues would be made available to VA researchers and non-VA university researchers with IRB approved funded projects. The tissues would not be available to commercial entities.

Dr. Nettleman noted that tissue samples and paraffin blocks were collected in 1991 and 1992. She asked if the brain bank would be getting the veterans' consent to use these tissues. This would allow the bank to have paired specimens. Dr. Fiore stated that the current consent was for all tissues and all clinical data. It didn't address paraffin samples on a line-item basis. Dr. Fiore noted that once a patient is deceased, the samples could be available. But it would be good to inform the patient of the intention to use this tissue.

Dr. Haley asked about the manner in which the clinical information would be maintained. Would it remain in the VA data system or would it be extracted into a separate database? Dr. Fiore replied that the ALS registry has detailed clinical information on this disease per se. They will copy this data, bringing it over into their own data bank. They hoped to eventually access the Health Data Repository (HDR), which is part of the consolidated VA national database. This is not the case now. Right now, they have created case report forms. They would like to access records with longitudinal data and have asked for permission to access the veteran's VA data records.

Chairman Binns asked if they intended to coordinate their efforts with the Armed Forces Institute of Pathology (AFIP), e.g., identifying what samples they may have already, etc. Dr. Fiore stated that these discussions had not happened yet. As they were currently planning this initiative, they were not sure what to ask for from AFIP. Dr. Fiore also noted that AFIP was in a state of flux. He didn't believe it was the best time to approach AFIP. Ultimately, they hope to engage AFIP in this process.

Ms. Nichols stated they needed to have a website about this initiative. She noted that there were VSOs that could help distribute this information. She suggested that they set-up a 1-800 phone number for those veterans who were not in the ALS registry. This would allow for last minute donations. She noted that duty officers needed to be briefed about this program so that they know how to handle the processing of these donations. She stated that the effort for this type of tissue bank was first raised by Gulf War veterans and their family members, namely the families of Jason Wickham and Fred Willoughby. Dr. Steele noted that Drs. Fiore and Prasad had been involved in the collection of an ill Gulf War veteran's tissues earlier in the year and that they had done "double-duty" to make this happen.

Mr. Griffin stated that when the initiative for the Durham ALS registry was issued, several veterans called the 1-800 phone number. They were told that because they didn't have ALS, they didn't qualify for the registry. As they had other disorders, they asked about the programs for which they would qualify. They were told that there were none and asked to not call back. Several veterans in north and central Texas are registered in MS chapters. Mr. Griffin stated that there was a disconnect between VA and other government entities when it came to the connection between these illnesses and Gulf War service. He works with the North Texas Neurology Association. There are more and more Shepherd Air Force base MS veterans who have to seek care "downtown." Many veterans could provide Drs. Fiore, Prasad and Haley with the names of physicians treating veterans with Parkinson's disease and MS.

Gulf War VA Biorepository Trust

Anil R. Prasad, MD
Staff Pathologist & Clinical Director, Pathology Research and Development,
Southern Arizona VA Healthcare System (SAVAHCS)

Dr. Prasad discussed the specific arrangements being made to establish the collection and storage facility for the VA Gulf War VA brain bank. (See Appendix A – Presentation 11b.)

The meeting recessed at 10:35 a.m. for a break.

The meeting reconvened at 10:45 a.m.

Chairman Binns introduced Dr. Joel Kupersmith, VA Chief Research and Development Officer (CRADO). He also welcomed Dr. Timothy O'Leary, Director, VA Biomedical Laboratory Research and Development Service, and Acting Director, VA Clinical Science Research and Development Service, and Dr. William Goldberg, Gulf War Research Portfolio Manager, VA Office of Research and Development

Update on VA Gulf War research programs

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

Dr. Kupersmith discussed current VA ORD initiatives and budget. Since the Fiscal Year (FY) 2007 budget had not been passed yet, Dr. Kupersmith stated that VA was currently operating under a continuing resolution. He noted, however, that both the House and Senate had proposed the same amount of funding as in FY2006, which would be a functional drop of 3.8%. VA ORD was not sure how they would trim operations, but he believed that they could probably get away without much change. A big issue, however, is what will happen with future research budgets. They had hoped for a little better budget, but it didn't happen. Dr. Kupersmith believed that VA researchers would likely bring in the same amount of NIH money as previous years. VA was also addressing an issue in regard to relationships with private industry that related to intellectual property rights in connection with Phase III trials.

Dr. Kupersmith stated that the contract with UT Southwestern was a major undertaking, involving several contracting issues that were being worked out. The contracting process at VA is complicated and VA has had problems in the past that have overshadowed this process. Thus, everyone was being very careful in these negotiations. Dr. Kupersmith added that the negotiations seemed to be nearing resolution and he was pleased by the way that UT Southwestern and its officials had handled the negotiations. He believed that UT Southwestern will develop the best of research programs. He noted that work was proceeding with respect to tissue banking efforts as Drs. Fiore and Prasad had discussed. He invited Dr. O'Leary, who was involved in this effort, to answer any questions on the subject.

Dr. Clauw commented that the tissue banking effort and the manner in which VA had responded was impressive. This was not an example of the VA placating the Committee or Gulf War veterans. A world-class tissue repository was being established, which would be the envy of any academic medical center or system. Dr. Clauw thought that the patient advocates who had pushed this effort forward deserved a lot of credit, and the VA deserved a lot of credit for its response. The Committee and audience gave a round of applause.

As there were no other questions or comments from the Committee, Chairman Binns wished to point out one remaining and unnecessary point of friction. He stated that the Committee had received a recent VA ORD update on the Gulf War portfolio. He noted that VA ORD and the Committee had had previous conversations about the categorization of what should be and shouldn't be considered Gulf War illnesses research. He was pleased with the pending contract with UT Southwestern and the developing brain bank. There was no question that VA was meeting and exceeding the 15 million dollars that the Committee had recommended in the past. Therefore, he saw no reason to continue classifying non-Gulf War illnesses research as Gulf War illnesses research. He noted that pretty much all the ALS research was included in the portfolio, even though only 3 out of 15 studies actually involve Gulf War veterans. Chairman Binns stated that the Committee would provide Dr. Kupersmith and his staff with the Committee's analysis of the portfolio. He thought this would be a great time to do another "scrub," because there was no reason for the "padding of the numbers" to continue. Dr. Kupersmith indicated that they would certainly look at this matter.

Ms. Nichols thanked Dr. Kupersmith and ORD for listening about the need for the tissue bank. She stated that it was impressive that it was finally happening. She stated that Gulf War veterans want to be acknowledged for having real illnesses. This is still being worked out. While it may not be a syndrome, Gulf War veterans are suffering from real illnesses. She stated that she would like to hear more of these clear statements from the Secretary and higher up in the administration. She stated that Gulf War veterans also wanted appropriate care, diagnosis, compensation and research. She stated that movement

had been made on research and compensation. However, there were still problems with coordination of their health care, as well the lack of a problem-solving central approach throughout the system. There was a need for coordination and training. Updating the clinical guidelines would help, but wouldn't solve all the problems. There are Gulf War patient representatives at each VA hospital. She stated that she had suggested to Secretaries Principi and Nicholson that there should be Gulf War veterans serving as liaisons in different VA facilities, working via a central committee. She stated that Gulf War veterans needed a committee similar to the Research Advisory Committee, but one that dealt with general issues of healthcare and administration. She also asked that veterans who attended the Committee meetings be offered the opportunity to acquire a hotel room through the Committee's room block and at the same rate. She hoped this would allow veterans to attend and participate in these meetings more. Dr. Kupersmith thanked Ms. Nichols for her comments about VA research and indicated that he would pass the other items along to those responsible for oversight of these issues.

Mr. Love stated that veterans had been given the opportunity to participate in events through 2001, noting the 1999 U.S. Centers for Disease Control (CDC) planning conference and 2001 federal Gulf War illness conference. These were normally coordinated between VA and DoD. After that, the military coordinating board was dissolved by the Pentagon and absorbed by the Deployment Health Support Directorate. Since then, Gulf War veterans haven't had a centralized governing body that provides for veteran participation. The process has been internalized. Mr. Love stated that there was a small governing body in place that was supposed to watch over the Directorate, but it did not involve itself externally. It was basically invisible. Mr. Love stated that there should be a secondary governing body that dealt with the Gulf War public. It needed to involve bidirectional communication and a centralized database. There is a need for an entity that was not specifically limited to issues of research. Mr. Love stated that there were still research issues, but there were broader concerns such as Environmental Health Coordinators not having access to information and lacking direction. There are a variety of veterans and other individuals who have valuable information to offer but have nobody with whom to share it. Establishment of this body would take the strain off the Committee, which is the "only show in town." The Committee then could focus on research while the second entity could deal with other concerns related to Gulf War illnesses. He asked if this would be something that Secretary Nicholson would consider doing. Dr. Kupersmith stated that he could not answer that question, but would pass the suggestion on to the Secretary. Dr. Kupersmith noted that the Committee could also pass this suggestion on to the Secretary as well.

Dr. McGill stated that, as a private physician, she would suggest that VA reexamine the "purple card" and number of approved visits to outside specialists when the local VA does not have the needed specialist on staff. She hoped that the VA could connect private and university physicians with veterans in areas where the VA had deficient services. Many of these non-VA physicians have provided care for veterans, but have not been paid for these services. She stated that these physicians would also be willing to give the VA feedback about what they had learned while treating Gulf War veterans.

Dr. Steele commented that one-third of the funded research in the Gulf War portfolio was related to ALS research, most of which was not specifically focused on Gulf War veterans. The analysis also showed that one-third of the funded research was focused on the kinds of issues that the Committee has discussed as being high priority research, i.e., Gulf War illnesses, other medical conditions affecting Gulf War veterans and the effects of Gulf War exposures. She noted that this was a higher proportion of well-focused studies than seen in earlier analyses. Most of these studies were funded in response to the 2004 and 2005 Gulf War RFAs. These RFAs were an effective way to get researchers focused on Gulf War illnesses and doing research in this area. Last year at this time, the Committee had heard from ORD staff that there would be a 2006 Gulf War RFA and a funded treatment research center announcement. Neither of these announcements was released. She wondered if there were plans for another Gulf War RFA, as

this seemed to be the way to get the best and most focused research. Dr. Kupersmith stated that ORD was waiting to see what happened in the negotiations with UT Southwestern with regard to Gulf War treatment studies and other research.

Dr. Melling stated that he was very impressed with the progress being made on the tissue bank. He noted that there had been major international cooperation among researchers in the epidemiology and biochemistry areas. He stated that he belonged to the United Kingdom's (UK's) Royal College of Pathologists and had not seen articles in their journal dealing with pathology studies such as the one Dr. Prasad described. He thought it would be good for Drs. Fiore and Prasad to share their achievements and plans for the future with their colleagues in the UK. Dr. Melling noted that, after the US, the UK had the second highest number of Gulf War veterans. As the years go by, opportunities there may also be being lost. Dr. O'Leary stated that the pathology field was a small community world-wide and that he expected that this would be happening.

Mr. Hardie commented that he had been involved in Gulf War veterans' issues for a very long time and this was his third meeting as a member of the Committee. He was consistently impressed with the work of the Committee and the interactions between the Committee and the VA. He also was deeply impressed with the research being presented at the meeting. He stated that he had been receiving the VA's Gulf War Review newsletter since its inception. He noted that it would be nice if the Gulf War Review included more of the information being presented at the Committee's meetings, as it would be useful to the Gulf War veteran community. He wished that there was more substantive information in the publication. He noted that the current editor was retiring and this might be a good opportunity to make this change. Discussion occurred about which VA department was responsible for the publication of the Gulf War Review.

Ms. Nichols asked that VA ORD consider expanding the ALS registry to cover other neurological conditions, e.g., Parkinson's, being seen in Gulf War veterans. She also suggested that a Gulf War cancer registry be established.

Mr. Love first apologized for not thanking Dr. Kupersmith earlier for the tissue database initiative. He appreciated this effort. Mr. Love then stated that it was his understanding that the Gulf War Review was being discontinued, following the retirement of its editor. He stated his concern about future plans to replace this publication and hoped that VA could put another editor in place. Dr. O'Leary stated that they could pass these concerns to those who are responsible for its publication.

Dr. Clauw stated that he saw parallels between the health care received by chronic fatigue syndrome/fibromyalgia patients and Gulf War veteran patients. As he struggled to help the University of Michigan determine how, as a system, it cared for individuals with common somatic conditions, e.g., pain, fatigue, etc., he would also encourage the VA to fund demonstration projects and different types of innovative ways to care for patients with these symptoms. If the medical community did a better job of this, he believed that Gulf War veterans wouldn't feel the way they do. This is true with fibromyalgia patients too. He stated that there was no healthcare system that did this very well, but VA had made an amazing turn-around in the last 15-20 years and was now the model of care. He stressed that VA had an opportunity and a better chance than anyone else to accomplish this. If VA was able to do this, he would love to see these research projects show up in the Gulf War portfolio because they would be very germane and relevant. Dr. Kupersmith agreed and thought Dr. Clauw's point was well taken. The VA does probably do a better job with respect to these illnesses. He had dealt with these illnesses in the private sector and the patients do not get very good treatment. He stated that there were programs supported by VA clinical funds that could address this.

Chairman Binns stated that the Committee would have time later in the day to discuss the question of what, if anything, it could do in terms of recommendations regarding the clinical issues raised. From previous discussions on this topic, he knew that the Committee was in the same position as VA ORD. Veterans have issues with these topics and bring them before the Committee because it is the "only game in town." The Committee has had to say that this is not within its purview, but there should be a vehicle to address these concerns. Chairman Binns agreed with Dr. Clauw, but believed in this case that there clearly were outdated guidelines and training materials for the VA clinicians with respect to Gulf War illnesses when compared to what current research shows. A first step would be to update the clinical guidelines.

Chairman Binns thanked Drs. Kupersmith and O'Leary for joining the Committee that day. He asked the Committee if it had any questions for Drs. Fiore and Prasad relating to the Gulf War Biorepository Trust.

Dr. Clauw noted that in neuroscience, especially in pain and sensory processing, there was accumulating evidence with respect to laterality of processes. He understood the tissue bank would be randomizing what side of the brain was collected. He was concerned that this would not serve neuroscience research well, because researchers were comparing more and more how the left and right portions of the brain were being activated. A lot of these processes do not occur bilaterally. He understood why they had set up the process the way they did, but this might cause problems for the researchers using the tissues. Dr. Prasad stated that the most important part of the collection process was the clinical data attached to each brain. He noted, however, that the value of any stored specimen depends on whether it can be used effectively and he would take Dr. Clauw's suggestion under advisement. Dr. Fiore commented that they hadn't addressed these concerns, e.g., the informatics that go into this process, in their presentations. He stated that this was simply a starting point and would be evolving over time.

Dr. Barlow commented that the sections collected were still very large. In terms of having array data for comparison, they would need finer resolution. She asked if there was a way to incorporate an XYZ coordinate system so that an investigator who found an abnormality could sample that same exact location in a series of brains for comparative analysis. Dr. Prasad stated that all of these images would be digitally-acquired, so the sampling location would be documented. He thanked the Committee for these types of feedback because it allowed them to account for all of the processes.

Dr. Meggs noted that the veterans had raised concerns that someone might pass away unexpectedly, but may wish to donate their brain to the tissue bank. He asked if any pathologist or medical examiner could do the autopsy and store the tissue in an appropriate manner with shipment arrangements being made at a later time. Dr. Prasad stated that standardization was one of the most important aspects of the collection process. They have set up standards as to where and how long a brain can be kept. The key is to snap freeze the brain as soon as possible. Dr. Fiore stated that this was an issue faced by other brain banks. The best solution was to post their specific protocols on the Internet. However, they can't have the freezing process at that site because the standardization would be entirely lost. They expect a sizeable percentage of specimens could be harvested and shipped. But there are several logistical issues that have to be overcome, e.g., obtaining suitable containers for shipment, etc. The only way they can approach this is to have a registered nurse and coordinator on call 24 hours / 7 days a week. It would be their responsibility to go to their screened list of pathologists across the country and see if one is able to get to the deceased veteran within 12 hours. However, the tissue bank was not willing to accept brains that had been handled in different ways because they would have to track how each specific brain was handled. They would get a marginal return on investment at that point.

Dr. Bloom noted that there was a growing literature of post-mortem salvaging in schizophrenia, depression and Alzheimer's disease. They originally thought the post-mortem interval was the really

critical factor. However, the time that the patient spends dying turns out to be more important. One of the standards in determining the degree of RNA sample preservation is the pH of the brain at the time of sacrifice. Dr. Prasad stated that this issue was addressed in the protocol.

Dr. Haley commented that collection of ALS specimens should happen quickly. However, it would be more difficult to collect good brains from those individuals with Gulf War illnesses. This is because they don't die in a predictable way and it will be harder to find them. He noted that AFIP collected tissues for five years following the Gulf War. It was likely they had brain tissue from ill Gulf War veterans. He suspected, however, that the tissue was formalin-fixed. He commented that DNA and RNA samples might be problematic, but wondered if this tissue would be useful for other research purposes. Dr. Prasad stated that a lot of tests could be done utilizing formalin-fixed tissue, including immunohistology, stains and examination of axonal morphology. While RNA extraction was problematic, DNA could be extracted from formalin-fixed tissue. Dr. O'Callaghan commented that there were several recently published protocols and commercial regents available for proteomic research on formalin-fixed brain tissue. Dr. Fiore interjected that tissue banks and investigators had come to a consensus that snap-frozen tissue was considered premium tissue. The current demand is for this type of specimen. While there is utility for formalin-fixed tissue, it is generally abundant in tissue banks. Dr. Prasad stated that the key to using a formalin-fixed block of tissue was knowing where it came from and how it was fixed.

Mr. Smithson noted that the VSOs could be a tremendous help in promoting the program and possibly recruiting actual donors. Dr. Fiore indicated that he appreciated the resources that had been shown to them and that they intend to follow-up sooner, rather than later, on this issue.

Ms. Marguerite Knox, a Committee member, commented that this appeared to be a world-class tissue bank. Dr. Fiore noted that it was a world-class idea that they hope to develop into a world-class tissue bank. Ms. Knox noted that it appeared that the funding went into acquiring the equipment and was being set-up as a resource that could be highly leveraged. Dr. Fiore agreed, noting their hope to expand the type of tissues being collected. Ms. Knox noted that there was a new product on the market called RNAlater that allowed one to preserve the RNA from the tissue being collected. Dr. Prasad stated that the protocol called for collecting tissue in RNAlater. Ms. Knox asked if they had a website that could be accessed to see what tissues were available or communicate with the investigators. Dr. Fiore stated that they have a private internal website now for the planning committee, but will be establishing a public face to this website in January or February 2007. Right now it is simply a scientific workspace for the planners.

Mr. Love noted that many veterans could not pay for an autopsy. He wondered if a grant proposal could be put together to help pay for these procedures. He also suggested that this program be coordinated through the environmental health agents in the VA facilities. Dr. Fiore stated that the funding for the brain bank also included monies to cover the cost of collecting the tissue (travel, removal of tissue and limited autopsy, if appropriate). He indicated that they hadn't thought about utilizing the environmental health agents, but appreciated the suggestion.

Dr. O'Callaghan asked if collection of tissue was stereotactic, allowing for coordination of the samples. Dr. Prasad stated that the digital imaging being used wasn't as specific as stereotactic coordinates. However, they could do a limited grid, which would allow them to localize the specimen slice. Dr. Fiore commented that brain banking was difficult and the procedures vary from facility to facility. Centralization of the whole process was necessary to achieve what Dr. O'Callaghan was asking. Standardization could only be achieved through tremendous quality controls and stringent protocols. They hope to achieve this, but Dr. Fiore acknowledged that it would be difficult.

Chairman Binns asked for any additional comments. The Committee and audience provided Drs. Fiore and Prasad with a round of applause.

Chairman Binns introduced Dr. Goldberg, who is also the designated federal officer for the Committee.

Dr. Goldberg noted that there should be copies of the Gulf War research portfolio on the back table and was willing to send anyone a copy if there were no copies left.

Dr. Goldberg reported that an issue arose with the placement of a notice of recruitment on the Committee's website for one of the clinically-orientated projects presented at the Committee's August 2006 meeting. He indicated that this raised IRB issues. He stated that, in order to address this concern as well as the Committee's concern that veterans were made aware of these trials, he was working to put all of the clinically-orientated projects, not just clinical trials, that involved recruitment of Gulf War veterans on NIH's clinical trials website (http://www.clinicaltrials.gov). This will provide a very public face for clinical recruitment efforts for all of these projects. This notice will be provided at the national level and should make it easier for the VSOs to notify veterans of these opportunities by directing veterans to a single website for this information. There are already a couple of Gulf War clinical projects on this website, which provides a summary of the project along with contact information. Dr. Goldberg will be contacting the Gulf War portfolio project principal investigators to obtain the information for the website. He stated that he hoped that this would be completed by the next Committee meeting. He hoped that by doing this that investigators, like Dr. Nancy Klimas, would have an easier time recruiting veterans for their projects.

Dr. Steele thanked Dr. Goldberg for addressing this issue. She noted that veterans had been asking for a long time about participating in studies. She stated that Dr. Goldberg's solution, putting the recruitment notices on NIH's clinical trials website, was a good solution. She also thought that, as it pertained to a research issue, the Committee could place a link to the NIH's website on the Committee's website. This would provide Gulf War veterans and interested investigators with information about research projects that are currently recruiting participants. Dr. Goldberg noted that NIH's website was able to receive notices about any clinically-orientated project involving recruitment, even those that might just involve recruitment for the collection of blood samples. He also stated NIH already addressed the IRB issues by obtaining a blanket IRB approval for the notices on their website. He indicated that VA ORD intended to make this a standard requirement for future projects that involve patient recruitment, that investigators will be required to provide the necessary information to submit the recruitment notices to clinicaltrials.gov. Dr. Steele stated that this was wonderful and she hoped that there would be an effort to make veterans aware of this resource. Dr. Goldberg agreed and stated that it required everyone, including VSOs, working together to disseminate this information.

Mr. Hardie asked if similar IRB issues would arise if the recruitment notices were placed in the VA's Gulf War Review. If it did, he suggested that the newsletter included a perpetual announcement that directed Gulf War veterans to the clinicaltrials.gov website. Dr. Goldberg thought that it would be possible to include an announcement directing veterans to the clinicaltrials.gov website. This wouldn't raise the need for IRB clearances or answering questions about who was promoting the particular study.

Mr. Smithson expressed confusion as to why VA could not promote a research project approved and funded by VA. Dr. Goldberg stated that the issue of how and where recruitment notices are placed rested on concerns about coercion. He stated that if VA would put such a notice on the VA's website, a veteran might be concerned that failure to participate in the study could jeopardize his or her access to VA health care and/or benefits. He stated that the Veterans Health Administration (VHA) was not comfortable with being a public notice site for recruitment for clinical trials. As NIH had created and received IRB

approval already for its website, it provided an easier, cleaner and more uniform way to publicize VA clinically-orientated projects.

Chairman Binns asked Mr. Smithson whether the VSOs would be able to assist in publicizing this development. Mr. Smithson indicated that this should not be a problem, noting many have websites and regular publications. He noted, however, that the publications did require lead time, which is generally 2-3 months ahead of publication. Dr. Goldberg stated that this was another advantage of going through clinicaltrials.gov. This would allow the VSOs to provide a standing announcement to interested veterans. The NIH website is updated on an instantaneous basis. VA would not have to continually update the list in other locations. Mr. Smithson agreed that it wouldn't be difficult to routinely include a reminder about this opportunity in these publications. He also agreed with Mr. Hardie's suggestion that such a standing announcement be included in the VA's Gulf War Review. Mr. Hardie noted that individual state departments of veterans affairs should be included in the efforts to publicize these opportunities to participate in research studies.

Chairman Binns asked Dr. Goldberg whether VA ORD would be publicizing the DoD RFA to VA investigators. Dr. Goldberg stated that he would be doing this. Besides being the VA' Gulf War portfolio manager, he is also the portfolio manager for VA's Parkinson's disease, Alzheimer's disease and ALS research programs. Thus, when he receives these types of notices, he forwards them to the VA researchers in that area. VA actively encourages all of its investigators to look for alternative funding sources to support their laboratories. VA acknowledges that it is not able to supply an individual investigator enough funding to maintain all aspects of their laboratories. VA is able to help start up their laboratories and provide a fair amount of core support. However, VA does not have the resources to fully support an investigator who has passed the initial stages of establishing a laboratory. Single merit awards can not support an entire laboratory. Currently, over 50% of VA researchers are also funded by NIH. This does not even begin to take into account the smaller foundation and private industry funding that is also being received. Chairman Binns stated that this was good news, because VA physicians were the ones most likely to be treating ill Gulf veterans and the DoD RFA was geared towards clinical and treatment studies. Dr. Goldberg indicated that he also would pursue having a notice of the DoD RFA distributed through the VA ORD's formal e-mail list to all VA research offices. The notice would encourage these offices to get word to their local investigators.

Ms. Nichols asked whether the VA would be able to place links to the clinicaltrials.gov website on the VA website. Dr. Goldberg indicated that this would not be a problem. He explained that the issue rested with placing the actual recruitment notice on a VA website. Ms. Nichols was glad to hear this. She also noted that there were veterans of other eras who would also benefit from this type of notice. She encouraged the Committee members who were affiliated with various VSOs to help publicize this website.

Mr. Love stated that it was his understanding now that the Gulf War Review would continue to be posted electronically. He suggested the directors of the individual VA medical facilities be notified about this effort and ask them to use their own public affairs offices to inform veterans of these opportunities. This would use each VA medical facility's budget instead of VA Central Office's budget. Dr. Goldberg stated that this would be a local IRB issue. The manner in which investigators are allowed to post recruitment notices are under the control of local IRBs. This is not mandated through Central Office. If they want to put a notice in their local newspaper, it would have to go through their local IRB. VA ORD didn't design it this way, but this is how the VA has decided to handle posting of recruitment notices. Dr. Goldberg stated that VA ORD hoped that investigators were already actively seeking to get recruitment notices in as many local outlets as possible.

Mr. Griffin noted that many veterans do not have access to the Internet and may visit a VA facility once every 4-6 months. He indicated that there needed to be thought given to getting the word out to these veterans.

With regards to the concerns being raised about the continuation of the Gulf War Review, Mr. Smithson noted that the latest edition of the Gulf War Review specially stated that the newsletter would continue. He asked if the Committee could confirm this, as well as clarify if it would continue only in the electronic form, with Dr. Mark Brown's office. Chairman Binns stated that the Committee could discuss during its business session whether the Committee should recommend that the Gulf War Review continue in a printed format for the reasons raised that day.

Public Comment – Day 2

Dr. McGill noted that there was a cohort of Japanese patients who were exposed to sarin in the subway terrorist incident. She discussed various symptoms experienced by these individuals and how these symptoms should be looked for in Gulf War veterans. She stated that she had started a new website to honor the Gulf War veterans who died between the wars: honorthenames.com. They are trying to find Gulf War-acquired illnesses, but this will take several years. Right now, they are focusing on the veterans who have died. They intend to go back and talk to the families as to whether the veteran was sick when he or she died. She stated that epidemiology studies had not been successful in doing this so far. She wasn't sure if it was possible to do it retrospectively, but it was the only method that was available to her in the private sector. She asked for referrals and help in publicizing this effort. She stated that this was a memorial website, which they hope will become a research tool that will connect deceased veterans' families with researchers.

Chairman Binns thanked Dr. McGill.

Mr. Kevin Smith, an audience member and Gulf War veteran, spoke to the Committee. Mr. Smith read and submitted a copy of his hand-written comments, which were typed and formatted for inclusion in these minutes. These comments can be found in Appendix B.

Chairman Binns thanked Mr. Smith.

Mr. Griffin thanked the Committee. He stated that the destruction of 970 sites during the Gulf air war, including nuclear research facilities and university research storage facilities, was rarely discussed. The wind was blowing south and through the sand. One needed to expand the map to At Ta'if and Jiddah and then circle back around to Bahrain and back up. Mr. Griffin stated that 48 SCUDs fell into the Kuwaiti Theater of Operations (KTO). He indicated that there was a cohort being tested for the enriched uranium inside the SCUDs. He noted that when it started raining, following the drought season, stuff was bubbling out of the ground. He stated that he worked in this area, along with several other troops. Many veterans were missing from the VA patient care lists since 1994 and he believed that many of these veterans were dead. He knew this based on an ad hoc study conducted by the veterans themselves.

Chairman Binns thanked Mr. Griffin.

Ms. Nichols noted Mr. Joel Graves' presentation at the June 2006 meeting about potential chemical exposures and exposure areas for Gulf War veterans. She stated that she had heard of no follow-up on this information. She asked whether there was follow-up information about the 1991-1994 cancer death data she presented at the same meeting. She hoped that DoD was being brought in to help analyze this

data. She stated that it seemed to have hit a dark hole, which was frustrating to Mr. Graves and her. She stated that DoD should be pushed to provide reports from the CCEP data. None of this data had really been researched to the extent it could be. This was why she mentioned the eye and ear testing. She stated that there needed to be reports prepared for the government-funded research studies that had never been published. With respect to accidents, Ms. Nichols expressed concern about the lack of interface with state and local public safety and health departments for their data.

Dr. Steele commented that there was a more comprehensive cancer research effort lead by Drs. Han Kang and Paul Levine that would capture the cases raised by Ms. Nichols, along with others. Dr. Steele noted that preliminary data from this effort was presented at a previous Committee meeting and that the findings would be finalized and published. As for the progress with funded government studies, Dr. Steele stated that this information was available online on Med Search. If there were no published studies available, this was noted. Chairman Binns asked what then happened to these unpublished studies. Ms. Nichols stated that Mike Hood had kept track of this information. She stated that there had been several funded studies that should have been published. If the results were not published, DoD should provide summaries. Dr. Steele reiterated that information regarding whether or not findings were published was available online, along with a summary of the results. She stated that the comprehensive annual reports required of each DoD investigator were also available online. Chairman Binns indicated that the Committee could provide Ms. Nichols with information about these websites.

Chairman Binns thanked Ms. Nichols.

The meeting recessed at 12:13 p.m. for a break.

The meeting reconvened at1:22 p.m.

Overview of Gulf War-related information on the RAC-GWVI website

Laura Palmer
Committee Coordinator, Research Advisory Committee on Gulf War Veterans' Illnesses

Ms. Palmer provided an overview of the information available on the Committee's website. (See Appendix A – Presentation 12.)

Committee Business

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

Dr. Steele gave a brief overview of the Committee's meeting and report schedules. (See Appendix A – Presentation 13.) She stated that resources had not allowed the Committee staff to complete the report as quickly as hoped. She indicated that the completion of the draft report was now slated for 2007. Dr. Steele invited the Committee members to submit ideas and suggestions for future meeting topics.

Chairman Binns stated that the secret to completing the 2006-2007 draft report was to clone Dr. Steele. He stated that he hoped Committee members, as well as those in the audience, would understand if Dr. Steele and staff would not be able respond to inquiries as quickly in the coming months.

Chairman Binns noted that a couple of issues were raised during the meeting that the Committee needed to address. First, he stated that there had been a suggestion that the Committee submit a recommendation

letter to the Secretary, suggesting that he consider creating an alternate advisory group or forum where Gulf War veterans could raise clinical issues. Chairman Binns stated that it was frustrating to the Committee and the veterans that the Committee could not address these concerns. He recognized that there were complexities in forming advisory committees, but suggested that there may be other formats that would meet the veterans' needs in this area. Chairman Binns noted that Dr. Kupersmith had invited the Committee to take a position on this issue. He didn't see anything that would prevent the Committee from doing this either.

Chairman Binns stated that the second issue that needed the Committee's attention was whether it should recommend the revision and update of the VA's clinical practice guidelines for medically unexplained illnesses, as well as the Veterans Health Initiative (VHI) series on Gulf War veterans' health, to reflect current scientific knowledge. While this was a clinical issue, it also reflected current research, which would provide the Committee with a basis to make such a suggestion.

Chairman Binns stated that the third issue that had been raised was the continuation of the Gulf War Review. He indicated that he could investigate whether there was any risk that it was not going to be continued, and if it was to continue, whether it would only be available electronically. If either was the case, the Committee might consider making a recommendation. Mr. Smithson agreed that the Committee needed clarification of the matter. Dr. Steele stated the Gulf War Review had only been available online for the past year. Chairman Binns stated that this could be a sign that it would continue.

Chairman Binns put the first issue, i.e., an alternative forum for Gulf War veterans to raise clinical concerns, before the Committee for discussion. Dr. Clauw asked whether it would be simpler to expand the charge of the Committee to address these issues, rather than creating a new committee that might not have the knowledge base that exists in aggregate here. Chairman Binns stated that the problem with changing the charter of the Committee was that it was a Congressionally-mandated committee. Expansion of the charter would require an act of Congress. Chairman Binns stated that, based on his conversations with veterans, the new committee should also be comprised mainly of patients and VA clinical staff. The need for outside advisors on these issues was not as great. Chairman Binns stated that he would not like having the Committee take on these responsibilities, as the Committee's "hands" were already full with the issues before it.

Dr. Melling stated that he was in agreement with Chairman Binns. He thought the Committee could address the concerns being raised by transmitting them formally to the Secretary. The Committee could inform the Secretary that these issues do come up at its meetings and the Committee is not able to address them to the satisfaction of veterans. The Committee then could request that the Secretary take the action that he felt that he was able to in order to meet this unmet need. The Committee would simply be flagging this as an issue that was in need of the Secretary's attention. Chairman Binns agreed that the Committee could leave open the resolution of the issue, just simply state the problem. Dr. Nettleman stated that it also was possible that these issues could be turned over to another existing VA committee. She noted that the VA did have committees whose activities related to quality improvement and patient outcomes. These committees simply may not have focused yet on the specific issues being raised by Gulf War veterans.

Chairman Binns asked the Committee if they liked this approach, i.e., the Committee put forth the problem to the Secretary and then list a few possible solutions, such as a subcommittee of an existing committee, creating an additional committee, etc. The final solution would be left to the Secretary. No objections were made. Chairman Binns indicated that he would draft language along these lines and distribute it for the Committee's review. Dr. Haley noted that, instead of creating a new advisory

committee, it would be less complicated to use or create an internal committee, which was comprised of VA department heads, to address these issues.

Chairman Binns asked the Committee about its thoughts on the VA treatment guidelines and VHI series. Mr. Smithson clarified that the VHI series was a compilation of continuing medical education courses addressing the various exposures that veterans receive. It is the content of the course on Gulf War veterans' health that needs to be reviewed and updated. Mr. Smithson noted that this program was created by the Environmental Agents Service, headed by Dr. Mark Brown. Dr. Clauw agreed that the guidelines were really outdated. Dr. Steele noted that the process to update these guidelines was somewhat complex. Dr. Clauw stated this was correct and noted that the guidelines were originally joint VA/DoD guidelines. He was not sure if this was still the case. Dr. Steele stated that it was. Chairman Binns asked if the Committee was comfortable with including a comment concerning this. The Committee agreed that this should be done.

With respect to the Gulf War Review, Chairman Binns stated that he would first investigate whether there was a possibility it would no longer be published. If it is a problem, he indicated that he would include a comment in the draft letter circulated to the Committee. Mr. Smithson suggested that a discussion occur with Dr. Mark Brown's office about the matter. Chairman Binns agreed that this might be an issue that could be addressed at that level. Mr. Hardie noted that the Gulf War Review was the only publication specific to Gulf War veterans' health concerns. And, as the Committee is the "only show in town" on specific Gulf War issues, it should comment on the continuation of the newsletter's publication. Discussion occurred about whether the electronic newsletter was reaching veterans.

Chairman Binns asked if there were any other topics or issues that the Committee would like to address. None were raised.

Chairman Binns stated that he had found the meeting to be very productive and exciting. He thanked Dr. Haley and the researchers at UT Southwestern for their presentations. Hopefully, the research conducted at this center, along with the Gulf War brain bank, the DoD RFA funded proposals, and continuing research projects will help move things forward for Gulf War veterans.

The meeting adjourned at 1:50 p.m.