Research Advisory Committee on Gulf War Veterans' Illnesses

December 12-13, 2005 Committee Meeting Minutes

U.S. Department of Veterans Affairs
810 Vermont Avenue, N.W., Room 230
Washington, D.C.

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 December 12-13, 2005, 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
Beatrice Golomb
Joel Graves
Robert W. Haley
Marguerite Knox
William J. Meggs
James P. O'Callaghan
Steve Robinson
Steve Smithson
Lea Steele

Committee Staff
Laura Palmer
Barbara LaClair

Guest Speakers
William Goldberg
Joel Kupersmith
Jonathan Gurland
Michelle Jones

Abbreviations

AChE	Acetylcholinesterase
AFIP	US Armed Forces Institute of Pathology
ALS	Amyotrophic Lateral Sclerosis
CDC	Centers of Disease Control
CFS	Chronic Fatigue Syndrome
CMI	Chronic multisymptom illness
CRADO	Chief Research and Development Officer (VA)
DoD	US Department of Defense
DU	Depleted uranium
EPA	US Environmental Protection Agency
FACA	Federal Advisory Committee Act
FY	Fiscal year
GAO	US Government Accountability Office
GWVIS	Gulf War Veteran Information System (VA)
HPA	Hypothalamic pituitary adrenal axis
IOM	Institute of Medicine
IRB	Institutional Review Board
MAVERIC	Massachusetts Veterans Epidemiology Research and Information Center
MoD	Ministry of Defence (UK)
MS	Multiple sclerosis
NIH	National Institutes of Health
NIOSH	National Institute of Occupational Safety and Health
NGWRC	National Gulf War Resource Center
OEF	Operation Enduring Freedom
OIF	Operation Iraqi Freedom
ORD	Office of Research and Development (VA)
OSAGWI	Office of the Special Assistant for Gulf War Illnesses (DoD)
PB	Pyridostigmine bromide
PTSD	Post traumatic stress disorder
RAC-GWVI	Research Advisory Committee on Gulf War Veterans' Illnesses
RFA	Request for applications
UK	United Kingdom
US	United States
USACHPPM	US Army Center for Health Promotion and Preventive Medicine
VA	US Department of Veterans Affairs
VBA	Veteran's Benefits Administration
VHI	Veterans' Health Initiative (VA instructional program for physicians)
VISN	Veterans Integrated Service Network (VA)

WRIISC War-Related Illness and Injury Study Center (VA)

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

US Department of Veterans Affairs
810 Vermont Ave., N.W. (Room 230) Washington, D.C.

Agenda
Monday, December 12, 2005

8:00 – 8:30	Informal gathering, coffee	
8:30 – 9:00	Meeting called to order Welcome, opening remarks, introduction of new members	Mr. Jim Binns, Chairman
9:00 – 10:00	Federal Advisory Committee ethics training	VA staff
10:00 – 10:15	Break	
10:15 – 11:15	Overview of exposures and health conditions reported by countries who served in 1990-1991 Gulf War Allied Coalition	Ms. Barbara LaClair, RAC-GWVI staff
11:15 – 12:00	Review/discussion of topics considered in 2004-2005	Dr. Lea Steele
12:00 – 1:00	Lunch	
1:00 – 2:45	Review/discussion of topics considered in 2004-2005	Dr. Lea Steele
2:45 – 3:00	Break	
3:00 – 4:30	Overview and summary: Wartime exposures in relation to chronic health problems in Gulf War veterans	Dr. Lea Steele
4:30 – 5:00	Public comment period	
5:00	Adjourn for the day	

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

US Department of Veterans Affairs
810 Vermont Ave., N.W. (Room 230) Washington, D.C.

Agenda
Tuesday, December 13, 2005

8:00 – 8:30	Informal gathering, coffee	
8:30	Meeting called to order	Mr. Jim Binns, Chairman
8:30 – 9:00	VA Office of Research and Development report on Gulf War-related funding announcements	Dr. Joel Kupersmith. VA Chief Research and Development Officer
9:00 – 10:00	VA Office of Research and Development report on recently-funded Gulf War research studies and VA Gulf War research portfolio	Dr. Bill Goldberg, VA Gulf War Illness Portfolio Manager
10:00 – 10:15	Break	
10:15 – 11:00	Status of VA Gulf War research program in relation to 2004 RAC recommendations	Dr. Bill Goldberg
11:00 – 12:00	2006 RAC Report	Dr. Lea Steele
12:00 – 1:00	Lunch	
1:00 – 1:30	Committee business	Mr. Jim Binns Dr. Lea Steele
1:30 – 2:00	Public comment period	
2:00	Adjourn	

Drs. Carrolee Barlow, Floyd Bloom, Daniel Clauw, Mary Nettleman and Hugh Tilson, who were appointed to the Committee on October 26, 2005, were not able to be present for this meeting, which had been scheduled prior to their appointments.

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 (RAC-GWVI) to order at 8:38 a.m. He thanked everyone for attending.

Chairman Binns stated that there were two major purposes of this meeting: (1) to review and discuss information presented to the Committee over the past two years in preparation for the Committee's 2006 report; and (2) to obtain information from the Department of Veterans Affairs' (VA) Office of Research and Development (ORD) on the outcome of the FY2005 Gulf War Illness Request for Applications (RFA), along with FY2006 plans and initiatives.

Chairman Binns noted that the Committee had received notebooks with the 2004-2005 meeting minutes. He expressed his appreciation of the work Dr. Steele, Ms. Palmer and Ms. LaClair had done in organizing the meetings for the past two years. He noted that these meetings had brought together experts representing all points of view on the subject topics, creating not only an opportunity to listen to these researchers, but also bring them together to talk with each other. He also expressed his appreciation at seeing VA ORD now fully participating in the Committee's discussions. He noted that it was beneficial for all involved to hear the same scientific data.

Chairman Binns introduced Dr. Joseph Francis, VA's new Acting Deputy Chief Research and Development Officer (CRADO). Dr. Francis provided the Committee with background information about himself. He is a general internist and geriatrician with a broad research background. He has been involved in health care administration for the past ten years, was Chief Medical Officer for one of VA's Veteran Integrated Service Networks (VISN) and was Director of Education and Research for a large private health system. Besides acting as Deputy CRADO, Dr. Francis is currently Director of VA's Quality Enhancement Research Initiative.

Chairman Binns stated that six new Committee members had been appointed by Secretary Nicholson on October 26, 2005. Due to the short notice, several (Drs. Carrolee Barlow, Floyd Bloom, Daniel Clauw, Mary Nettleman and Hugh Tilson) were not able to attend this pre-scheduled meeting. He stated that they would be involved in determining the Committee's 2006 meeting schedule.

Chairman Binns then introduced Dr. Jim O'Callaghan, who was appointed to the Committee in October. Dr. O'Callaghan is a Centers for Disease Control and Prevention (CDC) Distinguished Consultant and the Head of the Molecular Neurotoxicology Laboratory in the Toxicology and Molecular Biology Branch of the Health Effects Laboratory Division at CDC and the National Institute of Occupational Safety and Health (NIOSH). He received his PhD in Pharmacology from Emory University, held four National Institutes of Health (NIH) fellowships, and has received over ten Distinguished Achievement Awards of the Environmental Protection Agency (EPA) and CDC. He was a guest investigator in Dr. Paul Greengard's laboratory at Rockefeller University, as well as being an Adjunct Professor at the University. He has authored over 100 peer-reviewed publications, presented over 150 invited lectures, and serves on the editorial boards of the journals of *Neurotoxicology* and *Neurotoxicology and Teratology*.

Dr. O'Callaghan stated that he was honored and delighted to join the Committee, and thanked Chairman Binns for his introduction. Dr. O'Callaghan indicated that he was a "lab guy", spending the majority of his career conducting basic research into the effects of chemicals on the nervous system. He commented that there was still much to learn about neurotoxicology, and he was focusing on mechanisms and associated dysfunction at the molecular level. He was involved with CDC's "Research to Practice" program, which translates the practical aspects of his bench work to actual real-world application.

The Committee and staff introduced themselves to Dr. O'Callaghan and the audience.

Federal Advisory Committee ethics training

Mr. Jonathan Gurland and Ms. Michelle Jones, who are with VA's Office of General Counsel, provided training presentations to the Committee on the Federal Advisory Committee Act (FACA) and ethical rules which pertained to them as federal advisory committee members. Mr. Gurland and Ms. Jones provided members with two documents: (1) a brochure entitled "The Federal Advisory Committee Act: An Overview; and (2) a handout entitled "Ethics Rules for Advisory Committee Members Who Are Special Government Employees."

Chairman Binns thanked Mr. Gurland and Ms. Jones for their presentations.

The meeting adjourned at 9:59 a.m. for a break.

The meeting reconvened at 10:21 a.m.

Chairman Binns noted that there would be a change in the following day's (December 13th) schedule, in which the Committee would be working through the lunch hour so as to adjourn at 1:00 p.m.

Dr. Steele outlined the meeting's schedule and explained that the main focus of this meeting was to review materials presented to the Committee on topics covered over the past two years and to discuss findings and recommendations for the Committee's 2006 report. She noted, however, that the meeting would begin with Ms. LaClair's presentation of additional information for the Committee to consider in its review process. She said that when discussing Gulf War illnesses, questions often arise regarding the health of veterans from other Allied Coalition countries, as well as local populations. She stated that Ms. LaClair's presentation would help address some of these questions. She noted that this information approached Gulf War illness questions from an ecological perspective, analyzing patterns of exposures and health outcomes by country, and that this material might assist the Committee in describing the "big picture" of what exposures may be contributing to Gulf War illnesses.

Overview of Exposures and Health Conditions Reported by Countries who Served in the 1990-1991 Gulf War Allied Coalition

Barbara J. LaClair, MHA
Research Health Scientist, Research Advisory Committee on Gulf War Veterans' Illnesses

Ms. LaClair presented an overview of available information related to exposures and health conditions experienced by 1990-1991 Gulf War veterans from other nations, including the United Kingdom (UK), Canada, Australia, France, Czechoslovakia, and the Arab Coalition. (See Appendix A - Presentation 1.)

Dr. Robert Haley stated that it was interesting looking at this issue at this point in time. He noted that the similarity between the United States (US) and UK experiences were striking. Ms. LaClair agreed, and noted that there were striking similarities for both the troop exposures and health symptoms. She stated that one of the frustrations in doing this analysis was that the data from the various countries were not always comparable. Thus, a liberal approach was required to compare and interpret this information.

Dr. Haley asked whether any other country, besides the US and UK, had reported odds ratios for exposures in relation to defined multisymptom conditions. He stated that he had seen eight US studies and one UK study that had attempted to do odds ratios for risk factors. Dr. Steele noted that the Australian study had used defined symptom groupings and scores, and used adjusted ratios of the means for symptom scores in relation to exposures. Ms. LaClair stated that the Canadian study had used combined symptom groups as health outcomes, and that Chronic Fatigue Syndrome (CFS) was one of these groups. She stated that the study had calculated prevalence odds ratios in relation to grouped exposures but she had not included those in her presentation because they had not been presented in a way that was comparable to results from other countries. Dr. Steele noted that absolute rates of these defined outcomes in the Canadian study could be compared with the absolute rates in the Iowa Study.

Dr. Steele thanked Dr. Francis O'Donnell, with the Department of Defense's (DoD) Deployment Health Support Directorate, for helping Committee staff obtain a translated copy of the French Gulf War veterans study. She indicated that they had hoped the study would provide information about the prevalence of symptoms among French veterans. However, the broad nature of symptom questions used in this study and lack of a comparison group made the French results difficult to interpret.

Dr. Beatrice Golomb commented that attributable risk could be calculated using the odds ratio or risk ratio and rate of exposure to determine the amount of excess illness in Gulf War veterans related to a particular exposure.

Dr. Bill Meggs concurred that it was difficult to draw conclusions from this type of data, particularly for the countries who deployed small numbers of troops. However, he found it interesting that Denmark had a decreased exposure to pesticides and nerve agents and also lower neurological and musculoskeletal symptoms. He stated that conclusions could not be drawn from this, but that it was suggestive. Ms. LaClair agreed that this approach was nonquantitative and ecological. Dr. Golomb noted it could be made somewhat quantitative by looking at low and high estimates of odd ratios from different papers and using the best estimates from the deployed and nondeployed groups.

Ms. Marguerite Knox noted that Saudi Arabia had the third largest number of troops with 45,000 deployed. The Saudi study reported on only addressed 15,000 from the National Guard. Ms. LaClair stated that National Guard troops who had participated in combat had been compared to troops who had been in the Riyadh area.

Dr. Haley inquired about the Harvard School of Public Health study looking at the Kuwait population. Dr. Steele stated that this study hadn't been published yet. She indicated that the researchers have identified a 30% increase in mortality among Kuwaitis over the age of 50 who remained in the country during the war, compared to those who left Kuwait during the war. The researchers did not know the reason for this increase but that did not think it could be attributed exclusively to the oil well fires. They believed it may be due to the stress of being in the war zone. Dr. Steele stated that the study would also investigate health outcomes in the younger Kuwaiti population, and would obtain information about rates of chronic multisymptom illness (CMI) in this group.

Dr. Steele also said that there was little scientific information regarding the health of other local populations. She noted that there were scattered studies done in Bahrain and Kuwait, usually clinical reports using hospitalization data. She noted that shortly after the war, there were claims that Kuwait had suffered a great amount of excess illness as a result of the war. However, when data were reanalyzed, it was found that the associations weren't as strong as initially claimed because Kuwaiti hospitalization rates had already been increasing before the war.

Chairman Binns thanked Ms. LaClair for pulling this information together for the Committee's review. He stated that he was struck by two things: (1) one exposure may not be the only cause, but rather a combination of these exposures may be more toxic; and (2) the amount and significance of exposure to nerve agents appears to still be a contested issue, whereas pesticide exposures were less contested, except perhaps with respect to the degree of exposure.

Ms. Knox commented on the discrepancy noted with regards to the use of pyridostigmine bromide (PB) pills. She stated that troops were issued these pills before the war, and the decision to use them was to be made by each unit's commander. However, in practice, many individuals took the tablets without a command order. Ms. LaClair stated that the exposure data were self-reported, which could account for any usage or nonusage without regard to command decision.

RAC 2006 Report: Overview of Material Considered in 2004-2005; Review of Information Presented on Depleted Uranium

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

Dr. Steele presented an overview of topics reviewed by the Committee in 2004-2005 and the types of information that would be included in the 2006 Committee report. She then provided a summary of scientific information presented to the Committee that related to possible health effects of depleted uranium (DU) exposure. (See Appendix A – Presentation 2.) Information reviewed included presentations related to DU exposure levels in the Gulf War, animal studies evaluating the effects of DU, and information from epidemiologic studies relating DU exposure to the health of Gulf War veterans. A variety of presentations made to the Committee in 2004-2005 were referenced, including those provided by Mr. Al Marshall, Dr. Mark Melanson, Ms. Mary Ann Parkhurst, Dr. Terry Pellmar, Dr. Wayne Briner, Dr. David Barber, Dr. Johnnye Lewis, Dr. Melissa McDiarmid, and earlier presentations by Dr. Steele. The Committee then discussed unanswered questions in relation to DU and the health of Gulf War veterans, and recommendations to be included in the Committee report. .

Dr. Golomb inquired about the possibility of asking Dr. Han Kang to include a DU exposure question in his Persian Gulf War veterans' longitudinal study. She also indicated that without a better sense of where DU fit in the spectrum of things potentially related to veterans' health problems, it would be hard to say what priority this research should have overall, but thought that it was very important to the subset of veterans with high-level exposures. This should be balanced against research priorities for the broader group of veterans with multisymptom problems. Dr. Steele stated that the animal research in this area had been informative and that before she had seen the DU neurotoxicology studies it was hard to imagine a biological rationale for potential relationships between DU exposure and chronic multisymptom illness. These studies had demonstrated that DU had similarities in uptake and kinetic properties to other heavy metals and was potentially associated with brain and behavioral effects. .Drs. Golomb and Steele agreed that more data were needed.

Dr. Haley asked whether Dr. Kang's survey had asked questions regarding DU exposure. Dr. Golomb commented that DU questions had not been asked in the 1999 study. Dr. Haley stated that one of the problems with early surveys was that researchers used the wrong approach when drafting questions pertaining to DU. He stated that the researchers were thinking about the possible low-level radiation effects, not necessarily the possible chemical toxicity and inhalation/aerosolization of DU. He stated that someone needed to think through the "right" DU questions to ask on these surveys. Dr. Steele stated that the National Gulf War Resource Center (NGWRC) had developed several straightforward questions pertaining to veterans' activity and behaviors that were indicative of DU exposure in the field. She used these questions on one of her studies. Committee members discussed the Camp Doha fire, an incident that involved troop exposure to burning vehicles and munitions containing DU.

Mr. Steve Smithson asked if it would be worthwhile to make recommendations regarding Dr. McDiarmid's DU study at the Baltimore VA. Dr. Steele indicated that the Committee might consider recommending that the Baltimore study be expanded to include more exposed veterans and additional health outcomes. Another possibility was suggesting that a separate study be conducted to identify veterans with Level 2 exposures for comparison to veterans with no DU exposure. Dr. Steele noted that the local population may have also experienced lower-level DU exposures and that soldiers in the current war may have experienced similar exposures. Drs. Golomb and Haley noted that it would be difficult to tease out the effects of DU on the local population because there were so many different toxins in the area.

Dr. Meggs stated that better toxicodynamics and toxiokinetics studies could be conducted in this area. He noted Dr. Barber's findings that mice who had received single intramuscular injections of uranyl acetate continued to excrete uranium for 30 days, and those with implanted pellets excreted uranium indefinitely. He noted that not much was known about the health effects of inhalational exposure to DU. Dr. Steele said that Dr. Lewis had been the only one conducting inhalational studies on animals. She stated that Dr. McDiarmid may be assuming that because individuals with DU shrapnel did not exhibit measurable health effects, inhalational exposure would be expected to have even less health risk. Dr. Meggs stated it would be interesting to follow an individual with a high-dose inhalational exposure to see if DU had accumulated in the body.

Dr. O'Callaghan commented that in terms of metal neurotoxicity, findings such as Dr. Barber's that demonstrated that DU was retained in the brain and exhibited dose response effects were impressive. The brain doesn't like metals that aren't already there, and even if the metal is found at a very low level, there might still be brain damage. It is very typical to accumulate metals in the liver and kidney which can cause problems, but barely detectable levels of metals in the brain can cause substantial region-dependent damage. He noted that Dr. Barber's findings show distribution of uranium in different areas of the brain. He stated it was typical that even when metal levels are evenly distributed across brain areas, damage would vary by area due to the selective vulnerability of the brain cell types. He saw data on different DU levels by brain region, but not on differential effects of these exposures by brain region. Dr. Steele stated that Dr. Barber's group, who are continuing to study this issue, had considered this. She indicated that staff could talk to them about their findings on this matter.

Dr. O'Callaghan stated that it was very important to understand what brain regions are targeted and adversely affected in the long term so that neurological outcomes could be determined. Dr. Steele asked what damage outcomes would be expected if, as studies indicated, there was greater accumulation in the hippocampus and striatum. Dr. O'Callaghan stated that predictions might be learning and memory deficits, along with motor and cognitive deficits. He noted that, in neurotoxicology terms, it is common to see even distribution throughout the brain, but uneven effects. However, with data showing uneven distribution, one would want to get better pharmacokinetic and toxicokinetic data for these brain regions

to determine a variety of measures for adverse outcomes on the nervous system. He stated that there were many cases of devastating human neurotoxic exposures in which heavy metals were found in the urine, but low levels were detected in the brain. He said that finding detectable levels of uranium in the brains of lab animals was bad.

Dr. Golomb suggested that the potential relationship between acetylcholinesterase (AChE) inhibitors and DU exposures be investigated, considering there is evidence that AChE inhibitors may increase blood-brain barrier permeability. She noted that there was also evidence that multiple chemical sensitivity seemed to be associated with organophosphate exposures. This might also relate to findings that chronic inflammation in the nasal area could impair the "nose-brain barrier" function. She thought it possible that concurrent exposures might enhance the potential effects of DU. She noted also that there was evidence that aluminum exposure increased blood-brain barrier permeability and that other heavy metals like DU might have a similar effect. Dr. Steele mentioned Dr. Lewis' work demonstrating neurotoxic effects of inhaled manganese, and wondered if anyone in the Gulf War did not have nasal inflammation due to constant exposure to high levels of particulates in the region.

Diana Miller, an audience member and a neurotoxicologist with CDC, pointed out that the observed prolactin changes could be related to changes in dopamine levels in the brain as well as thyroid changes. These changes are seen with other heavy metals, like manganese.

Dr. Steele asked the Committee for its thoughts regarding recommendations related to DU and DU research. She referred to earlier ideas mentioned regarding expansion of the Baltimore cohort study and/or doing a separate cohort study of DU-exposed individuals, with a control group of nonexposed individuals. Dr. Golomb stated there was a need for epidemiologic data looking at the rates of chronic health problems, preferably with similar types of adjustment models as seen with the other exposure variables. Dr. Steele stated it was remarkable, after all this time, that there really wasn't much epidemiologic data on DU in relation to multisymptom illness.

Dr. Steele also asked about recommending animal research looking at the neurotoxic effect of DU. Dr. Golomb stated that she felt this was important, but wondered how important it was in terms of setting priorities for allocation of limited research funds. Chairman Binns stated that he shared Dr. Golomb's concern, because there was a limited research budget. However, he believed there were ways to address it in the report. First, one would wear their "scientist hat" and identify what is known, along with gaps and needs in this area of research. However, one would conclude by prioritizing these competing scientific needs in relationship to the needs of the majority of ill Gulf War veterans.

Dr. Meggs stated it might be beyond the Committee' province, but noted that DU was not going away. He stated that there would be subsequent exposures, which needed to be looked at by DoD beyond the Gulf War illnesses problem. He stated it appeared the percentage of veterans with significant DU exposure was too small to be a major factor in the 25% increase of symptoms across the categories seen in the first Gulf War. Regardless, he believed it was a very important toxin for the military to be "on top of" in the future.

Dr. Steele noted that the U.S. Armed Forces Institute of Pathology (AFIP) researchers had started to look at tungsten, due to the discussion of phasing in tungsten alloys and phasing out DU. She stated that some of the researchers have found that tungsten alloys are more problematic than DU. She also agreed that, if DU could cause chronic multisymptom illnesses, but required a substantial exposure to do this, it was unlikely that DU could be the primary cause of illnesses seen in the majority of Gulf War veterans. However, if it didn't require a substantial amount, simply requiring low-level DU exposure or DU as a cofactor with other exposures, then it might be a more plausible contributor to the problem. If low-level

DU exposure, alone, was a cause of multisymptom illnesses, we might expect greater indication that chronic multisymptom illnesses are a problem in the current war.

Dr. Haley inquired about the availability of reliable urinary assay methods for DU. Dr. Steele stated that this was a good question, and noted that the issue had been controversial. She stated that there were groups in Europe who claim that the 24-hour urine assay methods used by Dr. McDiarmid's group are not sensitive enough and believe there is a better assay. Dr. Haley stated that the Committee could recommend that a case control study be conducted, using a cohort of individuals with multisymptom illnesses or who have been exposed to DU. He noted that the most sensitive DU assay should be done. Dr. Steele suggested a variety of different assays could be tested. Dr. Haley agreed. He stated that the question needed an epidemiologic approach: Are people excreting DU, and if so, is this excretion related to their symptoms?

Dr. Steele opened the discussion to members of the audience.

Ms. Denise Nichols, an audience member and Gulf War veteran, suggested the Committee recommend looking at the DU DNA assay being conducted in Germany. She also suggested that, besides research concerns, the report should include clinical implications/recommendations that could be put into practice for Gulf War veterans being seen at VA. Suggestions might be to look at thyroid function or immune system changes. She stated that the research needed to be blended into clinical practice and that this was problem at VA. She agreed that the Committee should clearly identify scientific information needed with regards to DU.

The meeting adjourned at 12:34 p.m. for lunch.

The meeting reconvened at 1:34 p.m.

Review of Information Presented on Oil Well Fires and Petroleum Combustion Products

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

Dr. Steele presented a summary of the information presented in 2004-2005 on oil well fires and other petroleum combustion products. (See Appendix A – Presentation 3.) A number of presentations were referenced, including those made by Mr. Jeff Kirkpatrick, Mr. Warren Wortman, Dr. Jack Heller, Dr. David Cowan, Dr. Gary Friedman, and earlier presentations by Dr. Steele.

During the discussion of Dr. Friedman's presentation on oil well firefighters, Mr. Graves commented that the firefighters weren't living in the oil well fire plumes like the soldiers were. He stated that his unit was actually living in the plume for two weeks. Dr. Haley also noted that the oil well firefighters were a highly selective group of individuals. He stated that it would be expected that they would reflect a healthy worker effect. Dr. Steele agreed that the firefighters were not a perfect comparison group, but noted that it was rare to find any comparison group for isolated exposures encountered by Gulf War veterans and that she believed the information provided by this group was useful.

Following Dr. Steele's presentation, Ms. Knox suggested that one should go back and identify those individuals who are more prone to allergies and asthma. She stated that some soldiers' immune systems were stronger prior to deployment than others, and afforded them better protection to the various exposures experienced by the troops. She noted that individuals with asthma could be deployed to the

Gulf if their condition was under control. Dr. Steele stated that this was a good idea, but didn't know what post-exposure measurement might provide this information.

Dr. Meggs stated that Dr. Stewart Brooks (University of South Florida) had conducted a study that examined individuals who developed asthma following exposure to smoke or fumes. Dr. Brooks found that having an atopic disease was a major risk factor for developing asthma. Thus, if an individual had allergic rhinitis and was exposed to smoke or fumes, they were more likely to develop chronic rhinosinusitis or progress to becoming an asthmatic. He noted that most of the Gulf War studies looking at smoke exposures talked about asthma, but not chronic rhinitis. He stated that quality of life studies show that individuals with chronic rhinitis have a much lower quality of life compared to those with chronic asthma. Dr. Steele noted that the rate of chronic sinus congestion was commonly reported in both Gulf veterans and nondeployed veterans, so studies often didn't consider that symptom in connection with Gulf War illnesses. Dr. Meggs noted that there were well-documented associations between chronic rhinitis, depression, obesity, myalgias, etc.

Dr. Steele asked if Dr. Meggs knew of possible post-exposure measurements to determine an individual's susceptibility to inhaled substances. Dr. Meggs stated there were several ways to assess for present rhinitis, but wasn't aware of a way to assess for pre-exposure susceptibility. He noted these individuals' airways were considered "remodeled", which made them susceptible to an exposure.

Dr. Steele asked Mr. Graves if he could date the onset of his symptoms, or knew of anyone who could, from the time of his exposure to oil well fires. He stated that he couldn't say whether they developed in relation to exposure to oil fires alone any more than other exposures, e.g. pyridostigmine bromide (PB), by themselves.

Referring to Dr. Gregory Gray's research, Dr. Haley noted that, during the first year of their return, deployed Gulf War veterans had increased hospitalization rates for pulmonary problems. He said this was very important, because it was the time frame in which one would expect to see evidence of a large effect. He stated that this finding by Dr. Gray hadn't really been pursued further.

Dr. Meggs noted that Mr. Graves' comments about Gulf War soldiers being in a "toxic cocktail" needed to be kept in mind. He stated that the soldiers were exposed to various other toxins that the oil well firefighters were not. He commented that it could be the synergistic effect of these exposure combinations that explained why soldiers' health was affected, but not that of oil well firefighters. Dr. Steele agreed and stated that animal research examining the combination of smoke with other exposures was possible but that previous studies of combinations of exposures had not included oil fire smoke. .

Dr. Golomb stated there was a need to determine the apparent independent associations, and then look at subsets of exposures. Dr. Steele indicated that she would be presenting data on this later.

Dr. Steele opened the discussion to comments from the members of the audience.

Ms. Nichols suggested there were two sources of data regarding oil well fire exposure. These included: (1) Air Force evacuation records; and (2) Registry data collected upon return from the Gulf War. She stated that pulmonary function tests were conducted on returning soldiers. She noted that some of these troops had had pulmonary function tests before deployment to the Gulf. Dr. Steele stated that there were a couple of studies examining the pulmonary function of deployed and non-deployed Gulf war veterans. These studies had found no difference between the two groups. She stated that one unanswered question, however, was whether pulmonary function was different in veterans reporting chronic multisymptom illnesses.

Review of Information Presented on Vaccines

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

Dr. Steele presented a summary of information presented to the Committee related to the effects of vaccines. (See Appendix A – Presentation 4.) A number of presentations were referenced, including those made by Dr. Jack Melling, Dr. Beatrice Golomb, Dr. John Grabenstein, Dr. Phillip Pittman, Dr. Ya Fang Liu, Dr. Clare Mahan, and earlier presentations by Dr. Steele.

During the presentation, Dr. Haley voiced a concern about the credibility of government vaccine studies. Dr. Golomb stated that reported adverse effects from the anthrax vaccine were about .005%, whereas the actual rate was determined to be 10^4 higher with follow-up. She also noted that a recent newspaper article series described the underreporting of hospitalization rates among those receiving the anthrax vaccine. She stated that officials had reported 100 such hospitalizations, but the newspaper reporter had discovered there actually were 20,000 such hospitalizations. Dr. Haley stated that, out of all the subjects considered by the Committee, this area of research appeared to be censored most severely.

Dr. Steele asked how the Committee should address this issue in the report. Dr. Golomb suggested that the Committee point out the repeated objective discrepancies, and that the evidence seemed to contravene the published findings. She stated that there was no need to speculate about intent.

Ms. Knox noted that the anthrax vaccine received by troops in 1990-1991 was different than the current anthrax vaccine. She noted that the studies looking at the old vaccine found fewer side effects. It was suggested that more recent studies were not comparing "apples with apples." Dr. Meggs also noted that none of the studies looked at contributing effects of other exposures in relation to vaccines. Dr. Steele noted the Committee's discussion with Dr. John Grabenstein in April 2005, and the Committee's concern regarding the conclusions drawn from his group's work concerning hospitalization rates due to adverse vaccine effects.

During the discussion about squalene adjuvant in vaccines, Dr. Steele reported that Dr. Carl Alving's group was conducting a study that looked at whether ill Gulf War veterans had elevated squalene antibodies in comparison with healthy Gulf War veterans. She stated that the funding for this study had run out, but that the researchers were slowly, on their own time, trying to finish the work. She stated the staff would find out the status of this research before the Committee's report was issued. Discussion occurred about the differing assays used by Dr. Alving's and Dr. Pam Asa's groups. Dr. Golomb stated that Dr. Alving's group had published criticisms about Dr. Asa's findings before having data to support their opposing viewpoint. This created a conflict between the groups, and might result in a group's desire to reach a certain finding. Dr. Steele stated that Gary Matsumoto addressed this conflict in his book, *Vaccine A*. Dr. Haley suggested the need for a case control study conducted by an independent third party, which looked at the differing assays, along with vaccinated/non-vaccinated veterans. Drs. Golomb and Steele agreed that a blinded study conducted by a third party would be a good thing to do.

During the discussion about unanswered questions with regards to vaccines, Dr. Golomb commented that one of the Committee's central missions was to look at the excess illness occurring in Gulf War veterans. She stated that little was known about the illness complex from the current war. Dr. Steele noted that there was little animal research looking at the adverse effects of vaccines in combination with other exposures. Dr. Haley added that it might be beneficial to approach the question of vaccine effects from the opposite direction, e.g., specifically looking at the Rook hypothesis. Discussion occurred about looking for cytokine changes in ill Gulf War veterans. Dr. Haley thought it was worth summarizing this area of the literature in the Committee's report. He stated that concerns about multiple vaccinations had

generated this hypothesis. He noted that studies done in this area had been negative but that the hypothesis hadn't been ruled out completely. Dr. Golomb commented that the Rook hypothesis provided a departure point for public debate on something that should be addressed anyway, i.e., the role of cytokines in Gulf War illnesses. She suggested that the original departure point was not the central consideration, and that the larger issue—the role of cytokines—should be looked at systematically in light of current understanding, e.g. that there really isn't a pure Th1/Th2 dichotomy.

Dr. Golomb commented that there had been a couple of studies showing similar interleukin changes. Dr. Haley stated that the report should summarize these findings, since they provide the "other side of the coin" with regards to immunizations. Dr. Steele stated that different immune perturbations had been detected in different studies utilizing different methods and Dr. Golomb added that different exposures would be expected to lead to different cytokine shifts. Dr. Haley stated that, underlying all of this, was the use of different case definitions, which muddied things further. Dr. Steele agreed, and noted that the Peakman study may have been the strongest in terms of laboratory methodology, but that it had used a very nonspecific case definition.

Discussion occurred as to whether U.S. troops received the plague vaccine. Ms. Nichols stated that she had seen soldiers' records, showing the receipt of plague vaccine. Mr. Graves indicated that he believed that he had received the plague vaccine. Dr. Haley stated that, based on his understanding, the plague vaccine does not protect against aerosolized plague as would be encountered in a biowarfare situation. He stated that he had been told by General Blanck that plague vaccinations were not given to troops just because they were deploying to the Gulf War but that some troops routinely received the plague vaccine if they were being sent into an endemic area where they might be cutaneously exposed to infected animals. He said that British troops did receive this vaccination based simply on their deployment to the Gulf.

Ms. LaClair commented that the international data comparisons reviewed earlier in the day showed 22% of U.S. Gulf War veterans believed that they received the plague vaccine. Dr. Haley stated this might be attributed to misreporting by veterans, because many didn't know exactly what vaccinations they received. They simply knew they received vaccinations. Dr. Steele commented that it was difficult to find US studies of Gulf War veterans with complete shot records. She stated that the British had looked at UK veterans who had good records and found similar associations between vaccines and health outcomes among those with and without records. Dr. Golomb remembered that there were virtually no differences.

Review of Information Presented on Infectious Diseases

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

Dr. Steele presented a summary of information presented in 2004-2005 regarding the potential contribution of infectious diseases to chronic ill health in Gulf War veterans. (See Appendix A – Presentation 5.) A number of presentations were referenced, including those made by Dr. Alan Magill, Dr. Sam Donta, Dr. Quentin Deming, and earlier presentations by Dr. Steele.

During the discussion about Dr. Bourdette's study on leishmaniasis, Dr. Meggs stated that a follow-up study with more power was needed. Dr. Steele indicated that the assay used in the study had not been further developed. Dr. Haley commented that the group doing this study had had to contend with considerable challenges in moving this project forward but that they ultimately had not received additional funding and so had not continued this work. He stated that leishmaniasis was a good

hypothesis for Gulf War illnesses but that there was currently no way to diagnosis chronic leishmaniasis, unless one: (1) treated the individual and he or she got better; or (2) developed a more sensitive assay. However, the treatment for leishmaniasis (antimony) was toxic. Discussion followed concerning the difficulty of diagnosing viscerotropic leishmaniasis. Dr. Haley stated that the parasite "hides" in visceral cases, making it difficult to find, and that but it could even be difficult to accurately diagnosis an infected individual who was dying from hepatosplenomegaly. Chairman Binns asked what symptoms would be expected in a large infected group. Dr. Haley replied that there was thought to be an interaction between nutrition and the manner in which the disease presented itself. He stated that it wasn't known how a leishmaniasis epidemic would present in a group of well-nourished, healthy soldiers. He noted it probably would not result in hepatosplenomegaly and that it would be a difficult diagnosis, but the hypothesis should be tested.

Dr. Haley commented that he was part of a group, back in the late 1990's, that proposed a study that would treat a random sample of ill Gulf War veterans with amphotericin to see if they got better. He stated, without a more sensitive assay, this approach was the only way to determine if leishmaniasis was the cause of the veterans' health problems. Dr. Golomb was hesitant about this approach, but stated that, if there was any type of assay that could narrow the target population, it would improve the likelihood that true cases would be detected. Dr. Haley agreed, and wondered if Dr. Magill's group had been able to develop a better assay since he spoke to the Committee in February 2004.

Although she had been a co-author on the RAND infectious disease report (writing the chapter on mycoplasma), Dr. Golomb stated that she had reservations about the dismissal of the idea that an infectious disease was the problem faced by ill Gulf War veterans. She stated that she shared similar concerns about the possibility of ill veterans being affected by chronic leishmaniasis.

A discussion followed concerning various research studies that had been done on mycoplasma and Gulf War illnesses. Dr. Haley stated that there were two serological studies conducted by Dr. Lo. Dr. Golomb noted that serological assays are insensitive to mycoplasma. Dr. Haley stated that, even if the test was insensitive because of mycoplasma's ability to evade the host immune system, there should still be a higher prevalence of antibodies related to infection. He thought that Dr. Vojdani's study had not been blinded and was open to question because it had been conducted in a laboratory generating revenue from the test and that similar concerns were attached to Dr. Nicholson's study. He thought that Dr. Donta's study had not had those types of issues but did not directly address the issue because they didn't have a control group. The most valid studies, in his opinion, were Dr. Lo's serological studies. Dr. Steele disagreed, stating that if serological studies were not expected to detect intracellular mycoplasma infections, Drs. Vojdani's, Nicholson's and Donta's findings point to a testable hypothesis. Dr. Haley acknowledged this but thought the hypothesis was still untested with existing evidence and that the serological studies couldn't be discounted. Also, because mycoplasma is ubiquitous in the environment, Dr. Haley pointed out that cross contamination was a problem with PCR tests. Dr. Golomb stated there was a low quality of evidence supporting this hypothesis, but the evidence remained suggestive that mycoplasma could be a marker. She stated that, in her opinion, the mycoplasma infection was more likely a consequence rather than the primary cause of Gulf War illness.

To answer the question, Dr. Haley suggested that Dr. Joel Bateman's lab, which in his opinion was the best one for this testing, could be asked to do an analysis of case and control samples collected under strict guidelines to reduce contamination. Dr. Steele pointed out the lab results from Dr. Bateman's lab for the VA study had also provided anomalous results. While he believed there was no rationale or evidence for the hypothesis, Dr. Haley stated that a study should be done to put the issue to rest. Dr. Golomb disagreed that there was no evidence, but agreed that this research would not be at the top of her priority list.

During the review of Dr. Hyman's antibiotic treatment study, Chairman Binns recalled the input of Mr. Harold Nelson, an ill veteran who had been treated by Dr. Hyman, who reported that his health and quality of life had been restored by this treatment. Dr. Haley stated that he had treated an individual who developed severe renal failure following this treatment.

The meeting adjourned at 3:36 p.m. for a break.

The meeting reconvened at 3:51 p.m.

Upon return, Mr. Graves presented a chart which reflected an approach he had developed for organizing the material being reviewed by the Committee. (See Appendix A – Presentation 6.) Chairman Binns expressed his appreciation for Mr. Graves' organizational flow chart. He hoped that this type of presentation would stimulate discussion regarding the types of questions that most needed addressing. Mr. Graves stated that the purpose of the flow chart was to narrow the focus of interest.

Wartime Exposures in Relation to Gulf War Illnesses: Summary of the Evidence

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

Dr. Steele provided a presentation summarizing and comparing the evidence related to possible associations between the multisymptom illnesses affecting Gulf War veterans and Gulf War exposures, including psychological stressors. (See Appendix A – Presentation 7.) The presentation drew attention to differences between results of epidemiologic studies that did and did not analyze data in a way that controlled for confounding introduced by concurrent exposures. Using results from her own research, she illustrated how studies that did not apply appropriate statistical methods invariably found that almost all exposures appeared to cause Gulf War illnesses.

Mr. Robinson stated that DoD's Office of the Special Assistant for Gulf War Illnesses (OSAGWI) had a staff of database managers who took reports from Gulf War veterans, and asked about exposures similar to those identified by Dr. Steele. He believed that over 75,000 veterans were interviewed, and the information collected was used to direct OSAGWI's focus areas. Dr. Steele noted there was also a large amount of data collected by Dr. Han Kang's survey, which had a sample size of approximately 20,000. She stated, however, that Dr. Kang's analyses hadn't compared risk factors between sick and healthy veterans. Mr. Robinson asked if Dr. Kang's data was original, or based upon the information collected by OSAGWI. Dr. Steele stated that the data had been collected specifically for Dr. Kang's project. Because these data had been collected from a representative sample of Gulf War veterans, she stated that they would be more appropriate for research studies than the OSAGWI data.

Mr. Graves stated that he understood Dr. Steele to be saying that Gulf War illness may have been caused by a multi-combination of exposures. Dr. Steele agreed, noting, however, that in some studies, some exposures may only appear to be risk factors because they were linked to another exposure. Mr. Graves stated that he had long thought that PB and organophosphates may have caused Gulf War illness. Dr. Steele stated that this might be true for some people, but that different exposures and combinations might have affected different people in different ways. She noted that this was complicated question, and taking an overly simplistic approach could miss finding the answers.

Dr. Golomb stated that odds ratios and risk ratios are very important, but don't explain everything. If one had a rare, but powerful, exposure, it will be a very strong risk factor. However, it will have a low

attributable risk. Dr. Steele agreed, noting an example of this could be flea collars. Dr. Golomb stated that, in order to find the answer to this question, one would have to look at the differences in exposures and combine these with odd ratios. Dr. Steele stated that this was currently being examined, and attributable risks might be calculated if the necessary data are available.

Chairman Binns asked Colonel Frank O'Donnell, an audience member and staff member for DoD's Deployment Health Support Directorate, if DoD had changed the pesticide directives given to troops in the Gulf today versus that given in 1990-1991. Dr. O'Donnell stated that he was unaware of any change in those directives. He stated that both DEET and permethrin are being used. He stated that the problem that arose in the first Gulf War was the uncontrolled use of these pesticides. Dr. Haley asked if the high potency of DEET (75% in ethanol) was phased out. Dr. O'Donnell stated that this had been changed, noting that the current mixture ratio was 33% DEET. Dr. Steele noted the overuse of personal pesticides by 1990-1991 troops. Mr. Robinson stated that there was currently an emphasis on preventing the overlapping of pesticide spraying.

During Dr. Steele's preliminary summary of the evidence, Dr. Golomb questioned the animal studies pertaining to stress. She noted that researchers typically subjected animals to a physical condition, e.g. cold water, and called this "stress." Dr. Steele noted that the experimental physical exposures were never exactly like the conditions in the Gulf War. Dr. Golomb stated that the researchers had various concepts of stress, noting that Dr. Nisenbaum's study had referred to taking PB as "stress." Dr. Golomb commented that subjecting animals to cold water tests was not a pure psychological stress.

Dr. Diane Miller, an audience member and CDC neurotoxicologist, commented that this was the hypothetical constant of this type of research. She stated that researchers basically make manipulations and look at certain end points, e.g., looking at the hypothalamic pituitary adrenal axis (HPA) axis then determining if there is an increase in steroid levels. She noted that one does get into a problem by using the term "stress" in this type of research. Dr. Steele agreed, and wondered if it was valuable to make overly general statements about research findings in relation to any of the exposure questions. For example, psychological or physical stress in humans can cause acute symptoms and can also be associated with chronic symptoms among those affected by psychiatric illness such as PTSD. But it is unknown whether individuals exposed to potentially traumatic stressors who do not develop psychiatric illness have an increased rate of symptoms afterwards.

Mr. Robinson asked for clarification as to how the data presented on psychological stressors compare to clinical diagnosis data. Dr. Steele stated that they really relate to two separate questions. First, did psychological stressors during the Gulf War cause soldiers to become ill with chronic multisymptom illnesses? Second, upon return, what proportion of veterans developed a diagnosable psychiatric condition such as PTSD? Both questions are important. Chairman Binns noted that the general evidence on stress that had been referred to addressed a more theoretical question. i.e., can stressful exposures cause these kinds of symptoms? He stated that the data provided previously looked directly at the ill veteran population to determine if there was an association. This is where the psychological stressors did not relate, while theoretically they could relate.

Dr. Golomb noted that she was working on a similar project, and was seeing the same pattern with pesticides and PB being the most significant, followed by chemical warfare agents. Drs. Steele and Golomb discussed the methodology being utilized by Dr. Golomb in her project. Dr. Steele noted that unadjusted results were of limited use. Dr. Haley stated that the bar needed to be raised for the quality of future studies. Dr. Golomb stated that the report should make it clear that one should not use the modeling approach used by the Naval Health Research Center study, in which adjustment models included all exposures variables. Dr. Haley agreed, noting these approaches were two extremes that were

both misleading. Dr. Steele stated that, unfortunately, if studies utilizing these two extremes were discarded, there weren't many studies left. However, if concerns about confounding aren't adequately addressed, study results are questionable and generally indicate that everything causes Gulf War illness which, she noted, does not make sense.

Dr. Meggs commented that the day's presentations were a wonderfully clear and objective distillation of the literature in this area.

Chairman Binns asked Dr. O'Callaghan for his initial reaction, as a new Committee member, to the information presented that day. Dr. O'Callaghan stated that the most important point was making sure the appropriate research methods were being used. Studies using faulty methods were just wasting time. He found this to be a key point underlying the day's presentations and discussion. Dr. Steele noted that Dr. O'Callaghan would be able to provide insight into the best methods in laboratory science research. Dr. O'Callaghan acknowledged that expertise was needed in both laboratory and epidemiology methods in order to determine whether data and subsequent findings were valid or not.

Mr. Robinson stated it was critical to ask the questions that needed to be asked, and then answer them. He commented that ruling out certain things, while ruling in others, was vitally important, especially in determining the direction of research and finding treatments. He believed this review and approach was a great service for Gulf War veterans, and, once the information was teased out, would help veterans focus too. He stated that this type of review had never been done, and was great work.

Dr. Steele stated that the Committee's next report would draw from these conclusions and point out some of these findings.

Mr. Robinson asked whether the report would also indicate areas that needed further study because data are lacking. Dr. Steele stated that this was an important point and would be addressed in the report. For example, she noted that there is little research looking at DU exposure in relation to multisymptom illness. She stated that a basic epidemiological study was needed to provide information about Gulf War illness and DU. Once this information is available, additional decisions could be made concerning next steps.

Chairman Binns commented that, one-and-half years ago, he would have been in the camp that would be questioning the relevance of "rehashing" all of this information again. His views had changed, and he was pleasantly surprised by the amount of hard information collected and derived to answer these questions. He credited Dr. Steele with developing these insights.

Public Comment – Day 1

Ms. Denise Nichols addressed the Committee. She asked that the Committee consider holding at least one 2006 meeting outside of Washington, DC. She stated that many veterans were not able to attend the meetings and suggested coordinating the Committee meeting with a medical meeting to get interest from other researchers. She hoped that the Committee's next report would address clinical management implications. She also hoped that the report would be very specific as to the types of research needed in order to educate and direct researchers applying for the grant money. She also asked that the Committee ask the Veteran's Benefits Administration (VBA) to collect information about immune and endocrine disorders being seen in Gulf War veterans.

The meeting adjourned for the day at 5:11 p.m.

The meeting reconvened on Tuesday, December 13, 2005, at 8:35 a.m.

VA Office of Research and Development Report

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

Dr. Kupersmith gave an overview of VA research, the regulations that guide this research, and the progress made by VA in Gulf War illnesses research over the previous three months. (See Appendix A-Presentation 8.)

Dr. Steele asked if more could be said about the collaboration/pilot project with UT Southwestern listed on Dr. Kupersmith's slide, as well as the brain/tissue and gene bank proposals. Dr. Kupersmith stated that they were just being to work out the details for the initiative with UT Southwestern., and really couldn't talk about it any further detail because it was so preliminary.

Chairman Binns commented that he was pleased to see VA ORD proceeding with the Gulf War brain/tissue and gene bank projects. Mr. Robinson reminded the Committee and VA officials about a veteran who had offered to donate his brain to this type of organ bank. He stated that the veteran was not doing well, and was not expected to live much longer. He stated that the veteran and his family were still interested in donating his brain. With regards to the gene bank initiative, Mr. Robinson noted that the VA is holding serum samples, which were taken from 600 veterans before and after deployment to the Gulf.

Dr. Timothy O'Leary spoke to the Committee about the tissue bank project. He stated that it would take some time to establish because of its complicated nature. He stated that the VA currently had limited mechanisms with which to respond to offers such as the veteran mentioned by Mr. Robinson.

Ms. Nichols thanked VA ORD and the Committee for following up on the brain bank. She stated that the idea had been long discussed in the Gulf War community, and many would be happy to see it put into place.

Dr. O'Leary commented that VA ORD anticipated the tissue bank would include a variety of tissues from a variety of different individuals, including those who died with chronic multisymptom illnesses. He noted that specimens from controls would also be collected. He stated that they were still in the design process, but anticipated that the bank would be up and running within six months. The initiative would be run out of the VA's cooperative studies program, using a biorepository trust model developed by the Massachusetts Veterans Epidemiology Research and Information Center (MAVERIC). The physical tissue repository would likely be in Tucson, AZ, with management of consent running out of a coordinating center in Palo Alto, CA. It will be designed to operate nationwide.

Dr. O'Leary stated that they were also looking at establishing a DNA bank. They were considering the feasibility of sampling from Phase III of Dr. Kang's study, along with broader sampling strategies, in the development of this repository. He stated that the idea was to develop a way to understand why individuals exposed to a toxic insult might vary with respect to the effects of that toxic insult. He noted that there were a variety of nucleic acid alterations that were predictive of changes in metabolic pathways. Ultimately, they would be looking to determine what genetic factors are important in physiological responses to toxic agents. However, genetics would not be the whole story. He stated the time frame goal was the same, i.e., within the next six months.

Dr. Steele commented that these initiatives were wonderful. She asked whether investigators who had worked on previous efforts to create a VA brain bank were involved in this endeavor. Dr. O'Leary noted that MAVERIC had developed a multicenter tissue banking proposal, however, it was directed solely at brain tissue collection. He stated that VA had other tissue banking efforts underway, but these models weren't specifically applicable to this particular community. This was because the specimens were collected from much older veterans who were not as widely dispersed. In order to obtain an adequate number of specimens for research in a finite time, they will need to cast the net more broadly.

Dr. Steele asked if the DNA and brain tissue banks would be physically located at a centralized facility. Dr. O'Leary stated that the repositories could be separate. He noted that VA was a health care system in which a virtual bank, with multiple storage locations, was possible. He acknowledged that virtual banking was more likely with DNA than tissue, and might have problems when it comes to information technology. Dr. Golomb asked if other tissues were being considered for collection, as there were Gulf War veteran pathologies that went beyond the brain. Dr. O'Leary stated that they were considering this, and it would depend on the type of consent of the veteran. He noted that some states allowed pre-mortem consent while others did not, so obtaining the family's cooperation was very important.

Dr. O'Callaghan asked if they were considering sampling fresh brain specimens. Dr. O'Leary stated they were, and that the idea was to obtain fresh specimens in a number of different ways. Some samples would be considered useful for anatomical purposes, while others would be intended for biochemical and genetic analyses. Dr. O'Callaghan asked if this would be part of the sampling protocol under development. Dr. O'Leary said it would be.

Dr. Joe Francis, Deputy CRADO, noted a recent article in the *New England Journal of Medicine* about health information altruists and the ethical dilemmas of providing genomic information. He stated that researchers must rely on individuals being altruistic in providing this very personal information about their bodies. He couldn't identify a more altruistic group than veterans in this respect. He commented it was difficult to coordinate a national program such as genomics or brain banking. He stated that, given these difficulties, progress in this area was considered rapid. He stated they were developing a central institutional review board (IRB) process to overcome these hurdles.

Dr. Steele asked if there was a DNA banking component to the VA's ALS registry. Dr. O'Leary stated that there was, but that it was not intended to facilitate identification of potential donors outside those with ALS diagnoses and so was not specifically a resource for Gulf War illness research. He stated that the ALS registry also included the broader veteran community, i.e., it was not limited to the Gulf War. Dr. Kupersmith commented that the approach was to first ask what research questions needed to be answered, and then determine the manner in which the specimens should be collected.

Chairman Binns asked Dr. O'Leary if he would give a brief description of a DNA bank. Dr. O'Leary stated that the process starts with informed consent. The next step involved donations, which can be obtained in a number of different ways. One method can be as simple as obtaining cells from one's cheek. However, not much DNA can be collected via this method, so it was a limited collection technique and wasn't ideal. The second approach would be to take a blood sample, separate the white blood cells, and extract the DNA using various chemical approaches. Both of these approaches can be amplified using available technology. The third approach, which is the most interesting and most expensive, is to take the blood cells, infect them with an Epstein-Barr virus to make them immortal, and propagate them as a cell line. He stated that it was likely they would be looking at all of these methods. In some populations, it may be appropriate to establish cell lines. In other instances, some veterans may feel comfortable giving a donation in one form, but not another. He noted that this was a great gift from the veteran to the research community and nation as a whole.

Dr. Golomb asked if this project would focus on the nuclear genome. Dr. O'Leary noted that mitochondrial DNA would be present in the samples but the problem with mitochondrial DNA was that it can be different depending on sample site. He noted that mitochondrial DNA replicated at a different rate in lymphocytes compared to muscle cells. However, doing muscle biopsies was a separate issue. His perspective was not to do muscle biopsies at this time, but that this type of sampling could be part of a specific investigation. Dr. Golomb noted that mitochondrial DNA mutates 1000 time faster than nuclear DNA. She also noted that several conditions in which the Committee is interested, e.g., ALS and Parkinson's disease, have a known association with mitochondrial pathology. Dr. O'Leary stated that he anticipated the tissue collection would be relatively slow in comparison to the DNA collection.

Mr. Robinson asked if there was any way to inform the family of the dying veteran that VA was committed to moving forward on this issue, and that their input was valuable in getting this movement underway. Dr. O'Leary stated that VA absolutely was committed to doing this program, and encouraged Mr. Robinson to inform the family about it.

Dr. Meggs commented that any family could request an autopsy and the collection of certain samples. The sample collection may or may not meet the protocol standards down the line, but many preservatives and collection techniques are standard. Many people have done this in the hope that the specimen would be useful at a later time. Dr. Steele noted that the Armed Forces Institute of Pathology (AFIP) would accept tissue samples from Gulf War veterans for its repository. The only issue is obtaining an autopsy conducted at VA, which in turn raises the issue about the cost and who pays for it.

On behalf of the Committee, Chairman Binns thanked Dr. O'Leary for ORD's response to this issue.

Gulf War Update

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

Dr. Goldberg gave an update on: (1) the newly-established criteria used to determine whether a particular study would be included in VA's ORD Gulf War research portfolio; (2) VA's progress with respect to addressing the Committee's 2004 report recommendations; and (3) the status of the Annual Report to Congress on Federally Sponsored Research on Gulf War Veterans' Illnesses. (See Appendix A – Presentation 9.)

During the discussion of the Gulf War research portfolio, Dr. Golomb expressed concern about including studies that focused on stress, referring to several specific projects listed as part of the portfolio such as "Effects of Stress on Memory: Brain Circuits, Mechanisms and Therapeutics." Dr. Goldberg stated that alterations in processes associated with the HPA axis might be a factor in veterans' illnesses. He said it wasn't necessarily "the" factor or the cause, but that it should not be ignored. Dr. Golomb noted that the Committee had expressly recommended that stress studies no longer be funded with Gulf War research funds. She agreed that these were important areas of research, but that they were not recommended as the focus of studies funded as Gulf War illness research.

Dr. Goldberg stated that they were attempting to construct a very broad based portfolio of research on Gulf War veterans' illnesses. He understood that the Committee had its focus, and said that the Committee's advice was taken very seriously. However, VA also had a mandate to study, in their best scientific judgment, all aspects of illnesses affecting Gulf War veterans. Dr. Golomb pointed out that the purpose of having special Gulf War research money was that Gulf War veterans were experiencing conditions that are different than other veteran groups. She questioned Dr. Goldberg as to whether Gulf

War veterans had higher rates of PTSD than veterans from other wars. Dr. Goldberg stated that they were not looking at the HPA axis in terms of it causing PTSD. This was not the reason for including these studies in the Gulf War portfolio. These studies were included in case Gulf War veterans had altered immune or HPA function, which caused them to respond to their environments differently.

Mr. Graves acknowledged that "stressors" are a factor. Dr. Goldberg agreed, and stated that is why this type of research was included in the portfolio. Dr. Golomb stated that the Committee did not dispute that stress was an important area of study for veterans. However, it was not an important area of study for the special, and different, categories of illnesses experienced by 1990-1991 Gulf War veterans. She stated that the HPA axis alteration study related to PTSD.

Dr. Meggs commented that it would be reasonable to study differences in neurohormonal regulation among Gulf War veterans, and determine if there were biochemical markers for these alterations. Dr. Goldberg stated that this is why these studies were included in the portfolio. Dr. Golomb stated that it wasn't that she didn't think this was important research or that it would be lead to a dead end. She expressed her opinion that it just wasn't specific to 1990-1991 Gulf War veterans. Dr. Goldberg stated that the listed studies were specially looking at ill Gulf War veterans to see if they showed evidence of unique changes. Dr. Meggs stated that it appeared the researcher was going to look at biochemical measurements of neuroendocrine function in ill Gulf War veterans versus a control group. Dr. Golomb asked if both study groups were PTSD groups. Dr. Steele stated they were talking apples and oranges. She agreed with Dr. Golomb's general point, but pointed out that the first study listed ("Evaluation of Stress Response Systems in Gulf War Veterans with CMI") addressed biological stress responses in chronic multisymptom illness. The PTSD study being discussed was a separate project.

Dr. Goldberg stated that there was information of value to be gained from the disputed study. Dr. Golomb did not disagree that there was information of value, which would be especially important for the troops currently deployed in Iraq. However, it isn't the area of specific interest for the distinct health problems associated with 1990-1991 Gulf War service. Dr. Steele pointed out that the case control groups were PTSD vs. no PTSD, as opposed to Gulf War vs. non-Gulf War veterans. Dr. Goldberg stated that they would be working with the investigator to perhaps modify the protocol slightly to ensure additional data were collected that would be applicable.

Chairman Binns stated that he agreed with Dr. Golomb, but noted that the PTSD study began in 2003. He noted that VA's commitment to not fund stress-based research began in FY2005. Dr. Golomb thanked Chairman Binns for noting this point. Dr. O'Leary stated that, from his scientific perspective, the important thing was to figure out what was going on. He noted that stress had many different forms, including physiological forms. He stated these were issues that needed to be thought about and investigated. He recognized that there may be some difference in opinion between members of the Committee and VA ORD. However, he also thought it was important to recognize that the primary objective remains the same. These studies were not a major focus of the program, but weren't discounted. He stated, however, that he was aware of Dr. Golomb's concerns about inclusion of these studies in the portfolio.

Mr. Graves stated that he agreed with Dr. Golomb and the spirit of what she was trying to accomplish. He pointed out that it had been 15 years since the Gulf War, and for 12 or 13 of those years, stress was the primary research focus. He said that there had been ample opportunity and funding to study stress in the past but that since there wasn't a lot of money available for Gulf War research, the Committee just wanted to make sure it was now being used in a more targeted and strategic way. He stated that when he sees these types of studies sprinkled through the portfolio, he becomes concerned.

Chairman Binns noted that several of the studies which concerned the Committee were funded prior to VA's commitment to not fund new Gulf War stress research. He stated that the question was whether there were stressed-based studies funded in FY2005.

Mr. Graves noted that, when the Committee visited the East Orange, NJ, War-related Illness and Injury Study Center (WRIISC) in June 2004, he had been disappointed by some of their proposed studies and was further disappointed when these studies were funded. He stated that if nothing could be done about the previously funded studies, at least Drs. Goldberg and O'Leary had heard the Committee's concerns about future funding. Dr. O'Leary acknowledged this concern, but wished to make a strong distinction between PTSD and physiological stress associated with deployment. Dr. Golomb stated that the Committee was very familiar with that distinction.

Dr. Steele stated that there were a number of individual projects included among studies that had been newly-funded in FY2005 that the Committee might not consider to be ideal. The Committee's meeting binders included tables that summarized the focus of these studies, distinguishing between studies that addressed Gulf War illnesses and effects of exposures, psychological stress, ALS in the general population, and ALS in relation to Gulf War service. Overall, FY2005 Gulf War research funding totals included 17% for studies focused on psychological stress and psychiatric illness. She compared this with the FY2003 portfolio, for which over 50% of funding was for studies on psychological stress and psychiatric illness. Overall, she noted that the proportion of stress-focused studies had gone way down in this period. Dr. Goldberg agreed that this was the trend in the last RFA funding cycle.

Dr. Goldberg stated that part of this was due to a more refined RFA for 2005 proposals. The 2005 RFA provided much better direction and a list of suggested topic areas. He stated that having the list of topic areas helped the researchers refine their proposals to make sure that they were responsive. He hoped to get the next RFA out in January or February 2006 and requested input from the Committee on priority topic areas. The more direction VA ORD could give to the field researchers, the more likely they were to get the desired research projects. Chairman Binns welcomed Dr. Goldberg's invitation to help develop much more refined descriptions of the studies should be conducted. He noted for the Committee that the FY2005 RFA boldly stated that VA ORD was not funding studies based on the notion that stress is the underlying cause of Gulf War illnesses. Dr. Steele commented that this statement had worked, resulting in fewer such proposals.

Dr. Goldberg stated that, after finishing two funding cycles with a substantial number of approved projects, VA researchers were getting the point that this was a serious area of research. He noted that most of the proposals were coming from the Biomedical and Clinical Sciences services, which had a one-funded-proposal-per-investigator rule. He stated that an exception had been granted with regards to Gulf War proposals, allowing an investigator to apply for two grants. He believed there was a more positive perception among VA researchers that this was an area of research worth engaging in.

Besides recommendations as to what should be included in the RFA, Dr. Goldberg stated that he also would welcome particular recommendations with regards to proposals that shouldn't be considered. Mr. Graves expressed his displeasure with the telemedicine study listed in the portfolio. Dr. Goldberg stated that Dr. Kupersmith and he had spent considerable time looking at the various proposals, trying to determine if they provided information that would aid in understanding what was happening in Gulf War veterans. He noted that there were several studies included in last year's portfolio list that weren't included this year.

Dr. Steele pointed out to the Committee that information summarizing all projects included in the current Gulf War research portfolio was included in their binders. She noted that although the proportion of

newly-funded studies dedicated to psychiatric illness and stress studies had decreased, the portfolio still contained studies that the Committee would not consider to be Gulf War-specific. She noted that about one third of the portfolio monies were allocated to general ALS research not specific to the Gulf War. Dr. Goldberg commented that he wasn't sure he could separate a Gulf War veteran with ALS from anyone else with ALS. He stated that ALS had been service-connected for Gulf War veterans. He also guaranteed the Committee that all of VA's new ALS research was not included in this portfolio. He stated that there were a number of ALS studies that he felt were too far afield with regards to Gulf War veterans. Mr. Smithson clarified that ALS had not been presumptively service connected for Gulf War veterans. Dr. Goldberg agreed it wasn't presumptively service connected, but the ability to get a service connection had been streamlined. Mr. Smithson stated that there was a difference, and that he wanted to make it clear that VA could stop service connecting tomorrow without a presumption in place.

Chairman Binns stated that there were two issues on the table now: (1) What was funded under the FY2005 Gulf War RFA?; and (2) What is included under the Gulf War research portfolio, which covers multiple studies funded over the years and not necessarily studies that had been funded through the Gulf War RFAs? This leads to two separate questions: (1) Does the Committee agree with what VA is doing under the Gulf War RFA?; and (2) Does the Committee agree with their characterization of VA's overall Gulf War portfolio?

Chairman Binns asked if there was any discussion on the newly-funded projects. Mr. Graves suggested that future studies not focus on temperature extremes. He stated that heat wasn't an issue between October 1990 and April 1991. He stated that they fought in the rain. He acknowledged this would probably be a factor for the currently deployed troops, but not those in 1990-1991. Mr. Robinson noted that there were issues with high heat during the early build-up to the war (August to mid-October 1990), especially with soldiers wearing mop suits, but agreed that high heat was much more important with the current deployment. Dr. O'Callaghan commented that, in terms of neurotoxic effects, physiological and environmental factors such as temperature are increasingly recognized to play an important role. Dr. Golomb agreed.

Dr. Haley asked for clarification and justification for inclusion of certain studies in the Gulf War portfolio. The first study dealt with coagulopathy. Dr. Golomb stated that this was linked with CFS and fibromyalgia conditions. It involves reduced delivery of blood and oxygen to tissues. She believed that there was one published article that reported such abnormalities in Gulf War veterans. The second study involved experimental lung injury in response to heat exposure. Dr. Haley acknowledged there were issues involving oil well fires, but lung conditions weren't really evidenced in Gulf War veterans. Dr. Steele stated that Committee staff had classified this study as having only remote relevance to Gulf War veterans and that this study had been funded under the most recent RFA. Dr. Haley stated that this appeared to be an issue of the proposal review group not really understanding the focus of the RFA. Dr. Golomb asked if it was possible for the Committee to review the approvals. Dr. Goldberg stated that this wasn't possible. Dr. Golomb indicated that the point wouldn't to be to pick or choose the studies, but to help identify proposals that clearly weren't germane to Gulf War veterans' specific health issues. Dr. Goldberg stated that regardless of the system used, there would always be one project that the Committee and ORD would disagree on. He wasn't sure if there was a way to avoid this happening.

Mr. Robinson asked if Dr. Goldberg's comments regarding the Committee's review of proposed projects were based on his own opinion or a legal definition of the Committee's charge. Dr. Goldberg stated it was the legal definition of the Committee's charge. He stated that the Committee is charged with providing advice and recommendations to the Secretary. It was not to be involved in the peer review process. He stated that when Dr. Steele was participating in the review meetings, she was doing so as an

epidemiologist from Kansas State University. She was not there representing the Committee in her role as Scientific Director.

Chairman Binns commented that there was a case to be made on both sides as to whether the Committee should review the proposals. Agreeing to disagree on this point, he didn't believe there would be any disagreement that VA's review process for Gulf War proposals had been materially improved by having a member of the Committee with specific scientific expertise on Gulf War illnesses sit on the review panel. He noted that many of the less desirable studies funded in 2004 came out of the review panel without such an individual. He suggested that including more members from the Committee, in their independent scientific capacities, on these review panels might be a good thing. This was not because of a requirement that they be on the review panel, but because their contribution could be beneficial. Dr. Goldberg stated that the main criterion for serving on a merit review panel was having the appropriate scientific expertise.

Dr. O'Callaghan commented that he had previously served on a Gulf War merit review panel. He remembered being struck by the fact that it was unclear how the proposals related to the RFA. When he looked at the RFA, he was unclear as to the intended scope of the proposals. He had the impression that there had been no triage of the studies before they were reviewed by the panel. Dr. Goldberg stated that there was an agreement with VA field researchers that ORD would not use an abstract or short description to eliminate a project before a merit review committee had a chance to see the actual study being proposed. Dr. O'Callaghan commented then that it seemed the Committee needed to provide more specific RFA development advice.

Dr. Goldberg asked Dr. Steele for her thoughts on the manner in which the relevance issue was handled at the most recent 2005 merit review panel. Dr. Steele stated that relevance to the RFA had been a major focus for the panel on which she served. Dr. Goldberg stated that there had been extensive discussion of relevance, on many levels, by both panels in 2005. He indicated that the review process had been significantly altered from previous years, with which Mr. Robinson agreed.

Dr. Steele stated that the Committee had been provided with a separate summary of the twelve projects recently funded under the FY2005 RFA that was being discussed. She noted that there were no stress studies in this group, and 85% were Gulf War specific or related to effects of Gulf War exposures. She stated that the proportions were a remarkable departure from funding for studies resulting from previous announcements.

Dr. Haley asked Dr. Goldberg about the proposed projects that had not been approved for funding. He expressed concern that these projects may be much more relevant than those approved. Dr. Goldberg stated that the projects turned down were so scientifically flawed that they weren't salvageable. The merit review panel was given clear instruction on scoring, with an absolute cut-off score of 22. He explained that the scale range was 10 to 50, with 10 being the best and 50 being the worst. Scores of 22 and below are in good enough shape to proceed but may have some flaws. Scores above 22 were considered so scientifically flawed that it would be untenable to proceed with them at that time. He stated that the review panels provide the researchers with an explanation of what was wrong with the proposal, whether it was technical or design flaws, and that it could be revised and resubmitted. VA ORD has told the field that there is going to be another RFA, so the researchers are aware that there will be a chance to redesign and resubmit these projects. He stressed that no proposal was turned down because somebody didn't recognize its value. The merit review panels were instructed to evaluate quality of the projects, relevance to Gulf War veterans' illnesses, and relevance to the RFA itself. Dr. Steele commented that there weren't any borderline cases reviewed by the panel she sat on, and that there were scientific issues with the rejected proposals. She was encouraged to see a higher proportion of Gulf War-specific studies

funded under the last RFA. However, the goal now should not just be to fund studies that are relevant, but to fund studies that address key research questions that have a high priority for understanding Gulf War illnesses. Chairman Binns added that the vehicle for this was the RFA; and the RFA needs to list the most relevant topics.

Mr. Robinson commented that he was appreciative of steps taken by VA ORD to address the veterans' concerns. He indicated that he could articulate this now to the veteran community and let them know that their concerns were being heard, even though this is a scientific endeavor. Dr. Goldberg stated that when the criteria were distributed for comment in other ORD sections, a Gulf War veteran commented "so you are finally going to study my issues." He hoped that the Committee sensed that VA ORD is listening to the Committee's concerns, and that they are trying to focus on the illnesses affecting Gulf War veterans.

Mr. Graves inquired about standards for administrative overhead costs for research projects. Dr. Goldberg stated that the 12.5% allocated for this by ORD was very low.

Chairman Binns commented that the Committee had been fighting "this war", if you will, for four years, and that this was an enormous step forward in just a few months. He stated that current ORD officials had done everything they could do, short of putting a few more people on the merit review panels, given the point at which they came into the process. He noted that there was nothing grossly irrelevant that had been funded under the last RFA and 85% of the studies were relevant. He noted that Dr. Goldberg had not crafted that RFA, but would craft the next RFA to be more specific. He noted that the last RFA wasn't highly publicized, so hopefully the number of proposals received under the new RFA would be greater. Dr. Goldberg stated that they had tried to do a better job publicizing the last RFA when it was announced. The interesting thing was that the number of intents to submit and actual number of proposals was similar between the FY2004 and FY2005 submissions. He suspected that after two cycles of funding, there was a better perception of the chance of funding, and that they would see an increase in the number of submitted proposals.

Chairman Binns added that the Committee was disappointed to see that only $1.7 million had been spent on these new studies, as opposed to up to $15 million, which was what Secretary Principi had announced. Dr. Goldberg stated that whether this announcement applied only to "new research" was controversial as was the issue of "up to" versus "$15 million" in any particular year. Chairman Binns offered to show Dr. Goldberg a copy of Secretary Principi's public comments. Dr. Goldberg stated that ORD had made a firm commitment to spend $15 million on Gulf War research in FY2006, and that some of this money was earmarked for the tissue/DNA banks and the Gulf War treatment research center. He explained that this accounted for the difference between the $11.3 million listed on the portfolio summary sheet and the promised $15 million.

Chairman Binns stated he didn't want to belabor the point, but Secretary Principi had committed up to $15 million of new research beginning in FY2005. Going forward, he said that the Committee would hope that the percentage of new research would increase and that these studies would be relevant. He noted that the main disagreement at this point was how ORD was categorizing previous funding decisions in order to give the appearance of a higher dollar commitment to Gulf War illness research. He reiterated that there was agreement with the steps taken with respect to new research, and applauded the direction being taken by Dr. Goldberg.

Dr. O'Leary noted the Committee's perspective on this, but in terms of any clarification, ORD would have to defer to the Secretary. He said that VA shared the commitment of doing high quality research in this area and that they are trying hard to get there. VA has to meet a number of different imperatives and

consider advice from a number of different sources, such as the U.S. Government Accountability Office (GAO). The end goal for both VA and the Committee is to not fail these veterans.

Chairman Binns stated that his only suggestion was that the current VA ORD officials not feel obliged to defend the past. Dr. Goldberg agreed that there were things done in the past that were not appropriate. He stated that ORD had carefully evaluated what was currently included in the Gulf War portfolio and that it was, in their overall opinion, their best sense of a balanced and complete portfolio, looking at many of the illnesses and symptoms experienced by ill Gulf War veterans and possibilities for new therapies. He stated that the ultimate purpose of this effort was not to study Gulf War veterans' illnesses, but to find therapies to provide relief to these veterans. Dr. Golomb stated that the Committee agreed, and this is why the Committee was so intent on making sure that the focus was on understanding mechanisms, which should help ultimately to develop treatments.

The meeting adjourned at 10:11 a.m. for a break.

The meeting reconvened at 10:28 a.m.

Regarding the need for epidemiologic studies to determine the prevalence of serious neurological conditions in Gulf War veterans, Dr. Goldberg stated that no proposals had been received with regards to Parkinson's disease. There had been one proposal that would have looked at multiple sclerosis (MS), but it had been scientifically flawed. Dr. Haley asked if any data had been published by the Duke researchers with regard to the National ALS registry. Dr. Steele stated that a methodology paper had been published in 2004, and suggested getting an update on their research at a future Committee meeting. Dr. Haley agreed.

Mr. Graves commented that Committee criticisms concerning VA's research program were not directed at Dr. Goldberg personally. Dr. Goldberg stated that he hadn't taken it that way and understood that the concerns raised by the Committee were honest scientific and personal concerns about the direction of the Gulf War research program. He added that there didn't need to be universal agreement on every topic, but the more information that could be given to the field, the better the proposals would be. He looked forward to receiving suggestions from the Committee on research priorities for the next RFA.

Dr. O'Leary commented that although serious attention would be given to comments from individual Committee members there was more value and weight given to formal recommendations provided by the Committee acting in concert. Dr. Steele noted that the Committee had already assembled and provided lists of priority research topics to ORD in connection with previous RFAs. She thought that recommendations for the next RFA would include many of those, with some additional recommendations based on new information and recent discussions.

Dr. Goldberg proceeded with his presentation, providing the Committee with an update on the Deployment Health Working Group and its Annual Report to Congress on Federally Sponsored Research on Gulf War Veterans' Illnesses. He outlined the 21 Gulf War research priority questions established by the working group in previous years, and described how studies funded by the three agencies were included in the federal Gulf War research database.

Mr. Robinson asked if VBA/VHA data or epidemiology study data were used to evaluate the Annual Report's relevancy and priorities. Dr. Goldberg stated that epidemiology studies were the primary source of information. Mr. Robinson suggested also using the ICD-9 codes of Gulf War veterans within the VA system to determine what health problems were prevalent. Dr. O'Leary expressed two concerns with using that approach: (1) possible epidemiological bias due to differences in the populations enrolled in the

VA system; and (2) VA isn't the only agency involved in the process. Identification of priorities and review of the Annual Report were done by all three agencies (VA, DoD and HHS), which have different cultures.

Dr. Haley noted that the Committee had heard previous presentations about attempts to perform analyses using VHA databases. Dr. Steele commented that the Annual Report, in its current form, was not about how many people have a particular condition, but described the types of studies and levels of funding allocated for Gulf War research. But she agreed with Mr. Robinsons' general point that the highest research priority should be given to studies of conditions that were more common among Gulf War veterans than nondeployed veterans. Dr. Golomb added that Gulf War research should also focus on conditions and symptoms that don't currently have treatments. She noted that asthma may be elevated in this population, but there were already treatments available for this condition. She agreed that there was a need to fully describe the elevated conditions in Gulf War veterans. She noted that she, personally, probably wouldn't put pulmonary symptoms or diagnoses on the high priority list.

Mr. Smithson noted that VBA data don't provide a breakdown of conditions associated with claims that were denied, that is, information is only provided on conditions for which service-connection had been granted. Dr. Steele added that although this detailed information was not in the Gulf War Veterans Information System (GWVIS) Report, information could be obtained on the number of claims made by Gulf War veterans for any specific condition, including the number of claims approved, denied or still pending. Mr. Robinson commented that VA was tracking the current war's veterans by ICD-9 code. This presented a picture of the problems being seen in these veterans. He hadn't seen a similar breakdown for Gulf War veterans, despite there being over 365,000 individuals in the VA system.

Dr. Goldberg described the categories used to group the federal Gulf War research studies. Dr. Golomb asked whether "exposure studies" referred to studies that evaluate the impact of an exposure or determine the level of exposure. Dr. Goldberg stated that the original questions had been focused on epidemiology, e.g., "What is the prevalence of X?". However, the studies being assigned now to these categories may no longer be epidemiology studies but studies related to mechanisms and effects of exposures. He noted that the questions currently included on the list would be reassessed and that after this process, it was likely that even existing questions that remain on the list would need to be rephrased.

Chairman Binns asked if Dr. Goldberg would be the individual responsible for drafting the Annual Report. Dr. Goldberg indicated that he would have primary responsibility, but reiterated that the report was a multi-agency project.

Dr. Golomb suggested expanding Question 17 beyond the effects of short-term low-level exposure to PB, DEET, or permethrin, because there were other pesticides to which the troops were exposed. Dr. Goldberg agreed. Dr. Golomb noted that several of the new research proposals addressed the exposure combination of PB, DEET and permethrin. Dr. Goldberg stated that this may have become "the" combination, but the RFA could purposefully expand the combinations recommended for study.

Dr. Goldberg commented that the VA Gulf War research portfolio had included very few projects related to reproductive health and that this area was not being addressed by any agency's Gulf War research portfolio. Dr. Haley noted that early epidemiologic studies hadn't revealed much in this area, but more recent and better-designed studies had shown positive associations between birth outcomes and Gulf War service. Dr. Steele noted Dr. Araneta's previous comments to the Committee about there being no funding available for this type of research. Dr. Haley stated that the research questions in this area should be reframed based on current epidemiologic findings in order to determine where the critical issues are.

Dr. Goldberg stated there was a fair amount of work that needed to be done on the Annual Report, in addition to reviewing and restructuring the identified research priorities.

Dr. Goldberg described how data were encoded in the federal database that encompassed VA, DoD, and HHS information on Gulf War research. He stated it was more of a repository than a functional database. They currently are in the process of revamping it, and have sent the revised shell to DoD and HHS so that they can enter their data. VA will be the agency organizing all of the data. The next step in the process would be to analyze the data, and begin writing the Annual Report.

Dr. Steele commented that, in previous years, the category "Brain and Nervous System Function" always included both psychiatric and neurological studies, thus giving the impression that there were more neurological studies. She suggested that these studies no longer be combined in future reports. Dr. Goldberg stated that he would bring that suggestion to the Research Working Group subcommittee.

Dr. Meggs commented that Gulf War veterans were homogenized with the other veteran populations at VA clinics. He suggested having designated primary care physicians at each clinic that saw all the patients in the Gulf War cohort. He stated that this would provide a tremendous resource of information. He noted that these physicians would become more sophisticated with the diagnostic coding, but might also begin seeing patterns. Dr. Goldberg stated that the Gulf War database wasn't a patient record database, but rather a database of research studies funded by the federal government. He stated that neither the Research Working Group subcommittee nor ORD had the standing to advise VA clinical services how to practice medicine. Dr. Meggs noted that this might be a good thing for the Committee to recommend to the Secretary. Ms. Nichols asked whether this might fall under clinical research. Chairman Binns stated that it wasn't "research", but the Committee could comment on it. Dr. Goldberg stressed that the Annual Report was a report to Congress explaining how federal research monies had been spent in a particular year, along with accomplishments and future directions.

Ms. Knox expressed concern about removing psychiatric conditions from the report, because new science was showing that these were brain disorders with a biological basis. She was afraid something might be missed. Dr. Golomb stated that she understood Dr. Steele's suggestion was to categorize psychiatric and neurological research separately, not to remove psychiatric research completely. Separation of these categories would help to quickly determine how much money is going to each category.

Dr. Steele inquired about the status of the Deployment Health Working Group and its Research Working Group subcommittee. Dr. Goldberg stated that the Deployment Health Working Group met on a monthly basis. He identified several members including Drs. Mark Brown, Susan Mather, Kelly Brix, and Michael Kilpatrick. Dr. Goldberg noted that Dr. O'Donnell, a UK Ministry of Defence (MoD) liaison, and he himself attend many of the meetings as well. Dr. Goldberg stated that the Research Working Group subcommittee did not meet as often, but this would change when it was time to draft the Annual Report. He stated that the focus of the Deployment Health Working Group right now was on seamless transition and Operation Iraqi Freedom (OIF) and Operation Enduring Freedom (OEF).

Chairman Binns asked if the Deployment Health Working Group meetings were open to the public. Dr. Goldberg stated that they were not because this committee was not subject to FACA. Mr. Robinson noted that he was not aware of any publication of their recommendations.

Dr. Steele asked Dr. Goldberg to discuss the Gulf War treatment center RFA. He stated that because the RFA was in concurrence, the specific document couldn't be handed out and discussed page by page. However, he could talk about several aspects of the treatment center that were points of concern in earlier discussions. The first issue was the level of protected time for the center director. This had been set at a

minimum of 3/8ths time, and required a written commitment by both the medical center director and VISN director. He said there would also be the option of having a center scientific director, creating two high-level leadership positions. This mechanism should give strong leadership and keep the research enterprise going in the direction needed. Discussion followed about difficulties in obtaining protected research time for VA clinicians and the separation of clinical and research appropriations.

Chairman Binns asked Dr. Goldberg to provide the "big picture" of what the treatment research centers would be doing. Dr. Goldberg discussed various aspects of the treatment center concept and indicated that funding would be made available for up to 3 centers. One of the purposes of the centers would be to collect and analyze data on therapeutic interventions currently being used to treat Gulf War veterans in various locations. This would be a "clearinghouse function" of the treatment centers. He listed other aspects, including looking at treatments for other multisymptom illnesses, improving case definitions, determining proper measurement end points, and evaluating biomarkers and other approaches for monitoring effectiveness of treatments. He noted that a goal of these centers is to conduct pilot research on clinical interventions that could be used to lay the groundwork for larger multi- or single site clinical trials.

Mr. Robinson asked if Dr. Goldberg knew where these treatment centers would be located. Dr. Goldberg stated that he didn't, because they hadn't started receiving proposals yet. He would like to see them scattered, but this would depend on where the proposals come from. He suspected that proposals will be received from around the country. Mr. Smithson asked if there would be an effort to avoid concentrating them in one geographic location.

Chairman Binns clarified that these would not be treatment centers where veterans would go to seek special treatment for Gulf War illness. The purpose of these centers would be to develop information on potentially beneficial treatments and then do pilot studies. He stated that Dr. Steele had spent a considerable amount of time explaining what the Committee was recommending. This is something that is not commonly done in academia or government sectors. He was very pleased that the RFA reflects the concepts that the Committee had emphasized. Dr. Steele noted again that this would not be a center where veterans would be referred for treatment, unless they were involved in a pilot study. She stated that while dispersal around the country would be great, the main focus will be data collection.

Dr. O'Leary stated that that the treatment center research review panel would be looking at the following, in this order: (1) scientific merit, including program relevancy; (2) overlap and avoiding inappropriate overlap with other centers; and (3) geographic dispersion. He didn't think geographic location would be a major concern. He stated that the aim was to develop research ideas. Dr. Goldberg added that the geographic distribution tended to work itself out with the diversity of submitted proposals. Dr. Golomb noted that that the two WRIISCs were located close together (East Orange, NJ, and Washington, DC). Mr. Smithson stated that he had spoken with Dr. Mark Brown numerous times about the problems with accessibility to the WRIISCs.

Dr. Steele commented that it wasn't just the Committee saying this over the past few years, but that veterans and many others had been saying for many years that treatments for these conditions were badly needed and should have high priority. She thought that soliciting proposals for the treatment research centers was a huge step forward and was pleased to see it being done. Ms. Knox asked what treatments the centers would be assessing. Dr. Steele stated that these centers would be "casting the net" and determining what people are trying/using and what has been effective. Dr. Goldberg commented that this was the advantage of having three centers. It allowed for a wider variety of focus areas, while encouraging collaboration and cooperation between the study centers. Dr. Haley commented that the end

goal of these treatment research centers was to identify promising treatment that could be put into a collaborative studies program or clinical trial.

Dr. Goldberg stated that VA's Clinical Science Research and Development service conducted single-site clinical trials and that the Cooperative Studies program within that service conducted multi-site trials. This provided the vehicle by which the treatment research centers' findings could be investigated further. The treatment research center will provide the preliminary data for these larger clinical trials. Ms. Knox inquired about the VA's sleep study centers. Dr. Goldberg stated that the VA had two premier clinics, one located in San Diego and the other in Boston. He stated that neither center is currently doing Gulf War research but he had spoken with the group in San Diego about this possibility.

RAC Business

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

Dr. Steele gave an overview of Committee business and anticipated activities for the coming year, including the 2006 Committee report and possible areas of focus for 2006 meetings. (See Appendix A – Presentation 10.)

With respect to the 2006 report, Dr. Steele asked if the Committee wished to address topics in addition to those outlined. Dr. Meggs noted that the Committee had devoted a good part of a meeting to other complex multisymptom illnesses and how these illnesses may relate to Gulf War illnesses and believed that the report should address this topic. Dr. Steele agreed, and thought that the report should include information about the prevalence of these illnesses in Gulf War veterans and what areas of research on these conditions may be applicable to Gulf War veterans. Dr. Meggs agreed.

Dr. O'Callaghan suggested that the Committee address end-organ inflammatory responses underlying these multisymptom illnesses. He would like to see this area fleshed out. Dr. Steele agreed, and stated that this would a topic that the Committee would be focusing on in upcoming meetings. She stated that findings about this topic would not be included in the 2006 report since the information had not yet been reviewed by the Committee, but the next phase of the Committee work would address it. Dr. O'Callaghan noted that many of the symptoms affecting Gulf War veterans, like pain, have inflammatory components. This is an emerging theme in contemporary neuroscience.

With respect to future directions, Mr. Robinson commented that the Committee had a responsibility to help educate VA clinicians and there was a need to improve the Veterans Health Initiative (VHI) training series for Gulf War illnesses. He stated that the VHI guidelines were outdated and needed to be updated. Chairman Binns stated that perhaps the report could make a recommendation that the Committee's findings be communicated to VA clinicians and elaborate on how this might be done.

Ms. Knox questioned the likelihood of clinicians reading an entire bound booklet, but suggested summarizing key presentations and having researchers provide a continuing medical education course on the topics. Dr. Golomb noted that clinicians were poorly trained by the current VHI series and it might be advisable to require everyone to undergo this training again. Mr. Robinson stated that VA should recognize the additional information provided by the Committee in explaining Gulf War veterans' conditions. He stated that this was not apparent at this time, especially in light of the VHI series being so out-of-date.

Chairman Binns suggested asking ORD about the process for making such changes. Dr. Goldberg stated that VA ORD had no control over VA's clinical education. This is under the purview of Dr. Mark Brown's office. Mr. Robinson stated that Dr. Brown had promised him that he was rewriting the VHI Series but that it was unclear what the product would ultimately be, and the issue should be addressed with the Secretary through the 2006 report.

Mr. Smithson noted that the VA had gone out to other bodies in the past, including veterans service organizations, for input on these guidelines. He and Mr. Robinson stated that this issue had been raised several times to VA. Mr. Robinson said that Dr. Brown had admitted at the November 2005 Congressional hearing that review of the guidelines was two years late. Mr. Robinson would like to see the Committee have a guiding hand in this area. Mr. Smithson suggested a letter be drafted to Dr. Brown's office, requesting the status of this review process. Chairman Binns agreed that the Committee could do this. He stated that it wasn't officially part of the Committee's charter as a research advisory committee to address this. However, the Committee has been a focus for veteran comment in this area, because there are no other advisory committees. Dr. Golomb disagreed that this topic was not directly pertinent to the Committee's charter, because VA clinicians would be the ones submitting proposals and they needed to be properly educated on the direction of Gulf War illnesses research.

Chairman Binns asked about ORD's contact with the field investigators. Dr. Goldberg stated that there were monthly voluntary nationwide teleconference calls. He indicated that research administrators generally participated in the calls, not individual investigators. Chairman Binns stated that there was a concern that VA continues to send mixed messages to the field about the latest science in this area. He suggested bringing this issue to Dr. Jonathan Perlin's attention as Dr. Perlin has responsibility over both research and clinical areas.

Dr. Meggs suggested that the Committee provide a copy of the 2004 report to every member of the Institute of Medicine's panel that was reviewing the literature on Gulf War veterans. Dr. Steele said that IOM staff had told her that the report had been included in their review materials. Mr. Robinson stated that they may have reviewed it, but not considered it. Chairman Binns noted that they didn't say this, but rather that the Committee had a different assignment than that of the IOM panel. Drs. Meggs and Golomb stated that they still needed to review the peer-reviewed literature that informed the Committee's report. Chairman Binns stated that this point recently was made, formally and informally, to the chairman of the IOM Committee. It was suggested that she, as chairman, had the authority to expand the scope of the review. She indicated that she would look at whether to consider the DoD pesticide report.

Discussion shifted to future meetings and the possibility of providing an overall review for new Committee members. Mr. Robinson noted that leishmaniasis was becoming a major issue in the current deployment. He thought that it had been underreported in the first Gulf War, and focus should be given to this.

Members discussed the pros and cons of holding meetings outside Washington, DC. It had been suggested that this might increase veteran participation, but there was also a concern that it would limit the ability of senior VA officials to participate in the meetings. Dr. Steele noted that when the Committee did go to another location (East Orange, NJ), no veterans had attended the meeting. Mr. Robinson stated that work could be done to generate veteran interest in particular areas. Dr. Haley commented that the advantage of having VA senior staff present at the Committee's meeting was very important. Unless there was a compelling advantage to going somewhere else, he thought the Committee should continue to meet in Washington, DC. Dr. Meggs agreed. Chairman Binns stated that there was a reason to be in Washington, DC, so there would have to be a better reason for the Committee to meet elsewhere. Mr. Robinson stated that he was thinking along the lines of promoting the Committee's report, and getting its

contents out to the veteran population. He acknowledged that there were, however, more advantages to continued meetings in Washington, DC. He suggested that that there might be a better way to inform the veteran population about the Committee's work. Dr. Steele stated that briefing groups could be held at large VA medical centers across the center. Dr. Golomb suggested a one-page summary page with highlighted points.

Dr. Meggs noted Ms. Nichols' suggestion about holding a Committee meeting in tandem with a medical or scientific meeting. He thought it was a good idea but wasn't sure if those researchers would be interested in attending the Committee's meeting. Chairman Binns suggested presentations given by Drs. Steele and Goldberg at key VA medical centers. Dr. O'Leary stated that this would result in the Committee operating outside of FACA. Dr. Steele suggested that these would be public forums. Dr. Goldberg stated that the Committee's operating funds were for the Committee to meet, discuss and make recommendations. He stated that the funds were not for attending scientific meetings or having individuals go out and represent the Committee. Chairman Binns commented that he understood the general point that Dr. Goldberg was making but that there were instances where this type of activity would be appropriate for Committee staff in the execution of their duties.

Before moving on to Committee discussion, Mr. Smithson reported that the VA General Counsel's office had responded to an earlier question posed by the Committee about members providing expert medical opinions in support of veterans' claims. The General Counsel stated that these expert opinions are not precluded at the regional office and Board of Veterans Appeals levels.

The Committee began discussion of its suggestions for the FY2006 Gulf War illnesses RFA. Dr. Steele stated that Committee staff had, several times previously, assembled lists of bullets outlining research priorities for earlier Gulf War RFAs. These had been based on previous discussions and the Committee's recommendations in the 2004 report. Examples included: autonomic function in ill Gulf War veterans, differences in individual vulnerability to neurotoxins relating to genotype and enzyme levels, use of technologies such as genomic and proteomic methods and imaging technologies, and well-reasoned hypotheses related to other exposures. These areas might be more clearly defined and combined with ideas discussed more recently by the Committee such as an epidemiologic study related to effects of DU exposure or more in-depth research on the prevalence of undetected leishmaniasis.

Chairman Binns stated that the Committee should give as much input as possible during the meeting so that they could hear from members of the public on the ideas expressed. Dr. Haley wondered if it was necessary to adopt a recommended set of priorities for the RFA and give it to VA ORD today. Dr. Steele indicated that was not necessary, and it would be sufficient for Committee members to express their ideas and hold discussion in the meeting today. This information could then be distilled into a document that would be circulated for Committee review and approval before submission as formal recommendations to ORD.

Dr. Golomb suggested circulating the earlier list and inviting suggestions from the Committee. Dr. Steele indicated that there wasn't a single list available that compiled the earlier information, since those items had all been part of various drafts exchanged with ORD for different purposes. Dr. Golomb asked if it would be possible to create a document that incorporates all these recommendations, along with the suggestion of "other objective markers that may be associated with exposures and/or illness." Dr. Meggs asked if anyone had looked at markers of systemic inflammation, e.g., IL-6, or neurogenic inflammation. He suggested that this would be an important area to study.

Mr. Robinson asked whether the public meeting requirements were met by the Committee discussing publicly the basis and type of document it wished to create, then reviewing the specific information and

forming consensus, then coming out with the document. Dr. Goldberg stated that the findings and recommendations needed to be discussed publicly so there could be public input. Chairman Binns stated that the Committee's 2004 report and public discussions at meetings had provided the basis for previous RFA recommendations. These, along with discussions and recommendations made at the current meeting would constitute and help refine the list of recommendations to be offered for the upcoming RFA. He noted that, as discussed during Dr. Steele's presentation the previous day, the weight of available research pointed to neurotoxins such as PB, pesticides, and low-level exposure to nerve agents as being of greater interest than other exposures for the purposes of Gulf War research. Dr. Steele noted that the Committee could identify areas where more information was needed and make a determination of priorities and relevance. She also noted that the Committee's 2004 report contained general topics that the Committee had hoped would be included in previous RFAs, e.g., monitoring the health of Gulf War veterans over time to find out if there are excess rates of MS, Parkinson's' disease, etc. These topics are still important, and could be included in the current RFA.

Dr. Haley summarized areas mentioned as being important for Gulf War research as: (1) autonomic function; (2) predisposing factors, such as enzymes and genes; (3) proteomic and genomic analyses; (4) brain imaging studies; (5) hypotheses on other exposures for which there wasn't much information; (6) immunological studies; (7) birth defects; and (8) health issues for which there is no information, e.g., prevalence of MS or Parkinson's' disease.

Dr. Golomb suggested inclusion of research on the chronic effects of exposures labeled as high priority based on the Committee's previous meeting presentations and discussions. Chairman Binns agreed. While he thought DU, leishmaniasis, etc., should be examined, he indicated that higher priority should be given to exposures that have been shown most consistently to relate to Gulf War-specific effects. It was suggested that studies examining the mechanisms of these exposures be encouraged. Dr. Golomb noted that there may be other exposures that may be important, and these should be followed up as well. However, there are exposures that consistently show up as important, and they are of a particular interest. Dr. Golomb clarified that mechanism studies should focus on: (1) long-term sequelae of these high priority exposures; and (2) mechanisms of persistent or long-term effects of pesticides, PB, etc.

Dr. Haley asked if the Committee wanted to drive the research towards cellular mechanisms versus psychological types of studies, for example, PTSD studies. Dr. Golomb stated that she was afraid that the use of the word "cellular" might be misinterpreted and cause someone to eliminate something that was subcellular or organ-based, e.g. MRS studies. Chairman Binns suggested repeating what the previous RFA said about stress, and inquired if there were any other areas that the Committee thought should not be considered. Dr. Haley wondered whether it might be advisable to suggest there be no more studies focusing on the HPA axis, because this was often a code word for studies of psychological stress. Dr. Steele noted that research in this area could be important since, for example, the literature supported a connection of CFS with adrenal function and many believed HPA axis findings were one of the more promising areas of CFS research. Dr. Golomb suggested that it could be phrased to not include HPA axis studies except in association with its contributory role to effects of other exposures. Dr. O'Callaghan noted that, with respect to inflammatory response in all of the organs potentially involved in Gulf War illnesses, the HPA axis would be involved. Drs. Steele and Golomb agreed.

Chairman Binns asked if there was sufficient reason to jump ahead and anticipate the need for research in some of the areas that the Committee had just agreed should be discussed in 2006. He noted that this might allow researchers who are already looking at areas related to, e.g., inflammation, "to come to the party early." He noted the examples presented by Dr. Steele.

Dr. O'Callaghan commented that instead of looking at different symptoms, exposures and end points, if one read the minutes of previous Committee meetings and reviewed the symptomology and putative mechanisms, one could conclude that the inflammatory process was, in a broad sense, of great importance. He noted that there are end organ changes, certainly in the nervous and immune systems, that could be assessed and indicated that this is a common underlying theme of many of the reported symptoms, e.g., musculoskeletal, pain, allergic response, nervous system response, etc. Alterations in the neuroimmune and neuroinflammatory processes are important. There was information supporting a role for these processes in a variety of different biological systems and these could be studied more accurately with the benefit of animal models. Dr. Steele agreed. She noted that the list of bullets could include, as a priority of interest, studies involving alterations in neuroimmune/neuroinflammatory processes. Drs. Golomb and O'Callaghan indicated that they wouldn't limit it to "neuro" processes. Dr. O'Callaghan stated that there were lots of proinflammatory cytokine mediators within the organs that could not be sampled in living individuals as easily as serum markers. However, these mediators provided the basis for a lot of the different "itises." He mentioned Dr. Mohan Sopori's work that showed an exacerbated inflammatory response in sarin-exposed animals and noted that environmental factors could prime an individual toward an exacerbated inflammatory response, which is not a good thing to have. This could underlie many of the symptoms seen in Gulf War illnesses.

Dr. Steele asked Dr. O'Callaghan how he would summarize this point into a bullet. Dr. O'Callaghan suggested that the RFA seek research that was aimed at investigating the molecular and cellular basis of aberrant responses involving inflammation. Mr. Graves suggested delineating a more specific research bullet to address the neuroimmune and/or neuroinflammatory effects of low dose sarin/cyclosarin exposure with synergistic multicombination concurrent exposures.

Dr. Meggs noted that the problem with leishmaniasis was not exposure, but how the immune system reacts to the exposure. He stated that people who have an aberrant inflammatory response aren't able to clear the organism, and may develop the visceral disease. He believed this was a research area of interest, perhaps using *in vitro* tests to determine whether there was a Th1 or Th2 response. He noted that serology was not a good marker.

Chairman Binns asked whether the main concern, if leishmaniasis was considered an issue, was because it was an undiagnosed infection, i.e., a subclinical infection that is not apparent. Dr. Meggs stated that the question here was whether there is a subset of ill veterans who have a smoldering leishmaniasis infection, which can't be overcome, even though it might be a low level infection. He stated that one possible avenue would be to look at *in vitro* responses to a leishmaniasis challenge, using tests such as a lymphocyte proliferation assay triggered by leishmania antigen. One would test to see if there was a Th1 or Th2 cytokine response. Dr. Golomb noted that some Gulf War studies had included immune challenge tests, but not with regards to leishmaniasis. Dr. Meggs stated that if there was a Th2 response, then this could lead directly to a treatment. Ms. Knox asked if this involved the same principle as allergy shots and Dr. Meggs said it did.

Dr. Golomb asked if the Committee wanted to recommend specific studies in the RFA or specific categories of studies with examples given. Dr. Meggs stated that the lymphocyte challenge study could be built into another leishmaniasis study, an example being the PCR study. He commented that if the individual has cleared the organism and has an immune memory to leishmania, he or she should have a Th1 response. However, if they have a Th2 response that correlates with a PCR identification, they may have a potential problem, but also have a mechanism and suggestion for treatment. Ms. Knox asked if leishmania was cleared from the body completely, or was a chronic infection like *M. tuberculosis*. Dr. Meggs stated that he wasn't sure, but assumed that it was cleared because most people who get it have a self-limiting infection.

Chairman Binns said that another topic that might be included would be research that investigated whether chemicals associated with the high priority exposures or their secondary metabolites were retained in or excreted from the body. Dr. Meggs stated that it was known that organophosphates irreversibly bind to AChE. He asked if there are enzymes in neurons that are neutralized but aren't renewed like AChE. Dr. Haley stated that this depended on how often neurotoxic esterase is renewed, which he didn't know. Chairman Binns noted it would be wonderful to have the Committee's five new members involved in the conversation.

Dr. O'Callaghan noted that Dr. Carrolee Barlow had published a paper that showed that organophosphate delayed neurotoxicity had to be due to something other than neurotoxic esterase binding. He stated that these compounds were very reactive, and could bind to any number of substrates that may or may not be involved in long term illness or symptoms. Dr. Meggs asked if it was true that the mechanism of encephalopathy after organophosphate poisoning was not known and Dr. O'Callaghan confirmed this.

Dr. Steele asked how these ideas could best be captured into a succinct bullet and suggested that it might be worded along the lines of encouraging research investigations that look at retention of toxins or secondary metabolites that indicate prior exposure. Dr. Meggs mentioned earlier information presented to the Committee about work done at Lawrence Livermore Laboratories using MR-spectroscopy to detect very small levels of toxins.

Dr. Haley commented that it was important to recommend that all human studies of Gulf War illnesses utilize well-constructed case definitions. He pointed out that some of the studies were simply asking for volunteers, as opposed to including participants who meet criteria for a well-constructed case definition. Dr. Golomb stated that a case definition should not be specified until the mechanisms underlying these conditions were better known and that the mechanisms should define what a case is. Dr. Haley clarified that the researchers should be clear that they are using a case definition and describe what it is, but that a preferred case definition wouldn't be prescribed by the Committee. It was important that the study sample not be a group of volunteers and utilization of a well-constructed case definition should be a review parameter of study proposals. Dr. Steele stated that this might drive everyone to the Fukuda case definition, but agreed this was better than a list of volunteers who say they are sick.

Mr. Graves requested that a bullet be included regarding low-dose mustard gas exposure or mustard gas secondary metabolites. Dr. Golomb commented that mustard gas exposure was rare in the first Gulf War. Dr. Haley noted that Czechoslovakian troops had detected mustard gas in ambient air. Mr. Graves described an event in which he had been involved when a substance identified as mustard gas had hit his unit and others. Dr. Steele asked Mr. Graves if he was confident that he was exposed to mustard gas, since some of the symptoms he described suggested that other exposures might have been involved. Mr. Graves stated that he thought it was mustard gas. He noted that mustard was used in chemotherapy, which stops the growth of fast growing cells and that his hair fell out after this exposure. Dr. Golomb noted that hair can fall out after any major stress due to a phenomenon known as telogen effluvium. She indicated that she had heard of only one or two US soldiers being exposed to mustard gas during the Gulf War. Mr. Robinson commented that DoD verified one case of mustard gas exposure (PFC Fisher). With respect to the Czech mustard gas detection he said that DoD had concluded that it had been due to a fatty substance in the sampler that skewed the data. Coincidentally, he was contacted recently by a researcher who will be investigating a known mustard gas exposure in Iran. This study is being conducted though the NIH, and will be looking at the health outcomes of this particular exposure. He offered to put Mr. Graves in contact with this researcher.

Chairman Binns asked if it was being suggested that the gas that may have affected Mr. Graves' unit was not mustard gas, but perhaps sarin or cyclosarin. Dr. Golomb stated that mustard gas was a desiccant, and acted in a very different way than the substance described by Mr. Graves. Dr. Meggs suggested that low-dose mustard gas exposure may have different effects. Dr. Steele suggested that an option might be to recommend research on populations with known low-level exposure to chemical weapons (sarin, mustard, etc.) to investigate the long term sequelae of these exposures. Mr. Robinson noted that mustard shells had been found and could have been destroyed in demolition operations.

Chairman Binns commented that this discussion had been productive and Dr. Haley added that a good list of research priorities had been assembled. Dr. Steele agreed and indicated that the discussion had provided the information needed to put together the recommendations and that a draft document would be circulated for Committee review. (See Appendix B for final document.)

Public comment – Day 2

Chairman Binns invited members of the public to provide comments.

Ms. Denise Nichols submitted a letter provided by Ms. Julia Dykman, which had been submitted to the Shays Congressional hearing in November 2005. Ms. Nichols discussed results of a test that Ms. Dykman had recently taken that identified several heavy metals in Ms. Dykman's samples. She indicated that Ms. Dykman was willing to share these test results with the Committee. Ms. Knox inquired as to Ms. Dykman's location during the Gulf War. Ms. Nichols replied that Ms. Dykman served out of the hospital at Al Jubayl. Chairman Binns noted that the Committee had a general recommendation related to markers and that it could consider modifying it to include the possibility of investigating heavy metals. Dr. Haley asked if this was a type of chelation therapy or test. Ms. Nichols said no, that it involved special methods to pull out more heavy metal for testing. She stated that it was something that should be looked into, and suggested it may be a marker for inflammation.

Ms. Nichols circulated information about DoD-supported Gulf War research being done at Wright State University. One aspect of this research was the identification of a marker for predisposition to Gulf War illnesses. Ms. Nichols stated that she had been a participant in this research and shared her results with the Committee. Dr. Steele thanked Ms. Nichols and indicated that Committee staff was aware of the Wright State program and hoped to provide information on this research to the Committee.

Ms. Nichols suggested that research protocols require veterans to identify their unit, location and/or job in the military during the Gulf War. She stated that this requirement should be included in the guidelines for the research process. Ms. Nichols also suggested that research related to viral infection markers and subsequent treatment was very important. She commented that several Gulf War veterans received the polio vaccine, and it should be considered in the synergistic mix of exposures.

Ms. Nichols commented that an organophosphate marker study might be critical research for Gulf War veterans. This type of research might identify individuals who need to take special precautions to avoid future organophosphate exposures. She added that the ALS/MS/Parkinson's disease research should determine whether Gulf War veterans were experiencing atypical cases when compared to the general population.

Ms. Nichols asked that the draft resulting from the Committee's discussion of RFA topics be put on the Committee's website. Chairman Binns asked that Ms. Nichols relay to other veterans that this did not

have to be a consensus process, and that they could communicate any ideas they have that were relevant, regardless of whether the Committee's draft was posted or not.

Chairman Binns thanked everyone present for a good meeting and thanked VA ORD staff for their participation. Mr. Robinson thanked Committee staff for its hard work.

Chairman Binns adjourned the meeting at 1:10 p.m.