Research Advisory Committee on Gulf War Veterans' Illnesses

September 19-21, 2005 Committee Meeting Minutes

U.S. Department of Veterans Affairs
810 Vermont Ave, 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 September 19-21, 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
Joel Graves
Robert W. Haley
Marguerite Knox
William J. Meggs
Steve Robinson
Steve Smithson
Lea Steele

Consultant to the Committee
Jack Melling

Committee Staff
Laura Palmer
Barbara LaClair

Guest Speakers
Mihaela Aslan
Tim Bullman
Gary Friedman
William Goldberg
Han Kang
Joel Kupersmith
Paul Levine
Timothy O'Leary
Peter Peduzzi
Susan Proctor
Glenn Ritchie
Bellina Veronesi
Mark Witten

Abbreviations

AChE	Acetylcholinesterase
AFIP	U.S. Armed Forces Institute of Pathology
ALS	Amyotrophic Lateral Sclerosis
CFS	Chronic fatigue syndrome
CRADO	Chief Research and Development Officer (VA)
DoD	U.S. Department of Defense
EAS	Environmental Agents Service (VA)
FM	Fibromyalgia
FY	Fiscal year
GAO	U.S. Government Accountability Office
GIS	Geographic Information Systems
G6-PD	Glucose 6-Phosphate Dehydrogenase
GWI	Gulf War illness
GWVIS	Gulf War Veteran Information System (VA)
IOM	Institute of Medicine
IRB	Institutional Review Board
KKMC	King Khalid Military City (Saudia Arabia)
LOI	Letter of Intent
MOD	Ministry of Defence (UK)
MS	Multiple Sclerosis
NCI	National Cancer Institute
NIH	National Institutes of Health
NGWRC	National Gulf War Resource Center
OEF	Operation Enduring Freedom
OIF	Operation Iraqi Freedom
OPIDN	Organophosphate-induced delayed neurotoxicity
ORD	Office of Research and Development (VA)
OSAGWI	Office of the Special Assistant for Gulf War Illnesses (DoD)
PTSD	Post traumatic stress disorder
RAC-GWVI	Research Advisory Committee on Gulf War Veterans' Illnesses
RFA	Request for Applications
USGS	United States Geological Survey
USACHPPM	U.S. Army Center for Health Promotion and Preventive Medicine
VA	U.S. Department of Veterans Affairs
VHI	Veterans' Health Initiative (VA instructional program for physicians)
VOC	Volatile organic compound
WRIISC	War-Related Illness and Injury Study Center (VA)

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

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

Agenda
Monday, September 19, 2005

Time	Topic	Presenter
8:00 – 8:30	Informal gathering, coffee	
8:30 – 8:45	Meeting called to order Welcome, introductions, opening remarks	Mr. Jim Binns, Chairman
8:45 – 9:00	Exposures in relation to Gulf War illnesses: Review of topics covered in 2004-2005	Dr. Lea Steele, RAC-GWVI
9:00 – 9:15	Oil well fires and the health of Gulf War veterans: Overview and remaining questions	Dr. Lea Steele
9:15 – 10:15	Health evaluation of civilian firefighters who capped the 1991 Kuwaiti oil fires	Dr. Gary Friedman, Texas Lung Institute
10:15 – 10:30	Break	
10:30 – 10:45	Exposure to combusted petroleum products and particulates in the Gulf War	Dr. Lea Steele
10:45 – 11:30	Health effects of particulate exposures	Dr. Bellina Veronesi, U.S. Environmental Protection Agency
11:30 – 12:00	Discussion	
12:00 – 1:00	Lunch	
1:00 – 1:30	Exposure to solvents in the Gulf War	Dr. Lea Steele
1:30 – 2:00	Fuel exposures in the Gulf War	Barbara LaClair, RAC-GWVI
2:00 – 2:45	Jet fuel exposure I: Effects on the immune system	Dr. Mark Witten, Univ. of Arizona College of Medicine
2:45 – 3:00	Break	
3:00 – 4:00	Jet fuel exposure II: Neurological and behavioral effects	Dr. Glenn Ritchie, Battelle
4:00 – 4:30	Discussion	
4:30 – 5:00	Public comment period	
5:00	Adjourn for the day	

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

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

Tuesday, September 20, 2005

Time	Agenda Item	Presenter
8:00 – 8:30	Informal gathering, coffee	
8:30	Meeting called to order	Mr. Jim Binns, Chairman
8:30 – 9:30	Additional unstudied exposures of possible concern in relation to Gulf War veterans' health	Dr. Lea Steele
9:30 – 10:15	Gulf War illness symptoms in relation to troop location: Use of GIS spatial analysis	Dr. Susan Proctor, VA Boston
10:15 – 10:30	Break	
10:30 – 11:30	Update on VA research evaluating read-through acetylcholinesterase (AChE-R) levels in Gulf War-era veterans	Dr. Mihaela Aslan, VA New Haven
11:30 – 12:00	Discussion	
12:00 – 1:00	Lunch	
1:00 – 1:45	Mortality in Gulf War veterans in relation to modeled proximity to Khamisiyah demolitions	Tim Bullman, VA Washington, DC
1:45 – 2:30	Cancer in Gulf War-era veterans: Information from state cancer registry data	Dr. Paul Levine, George Washington Univ. School of Public Health
2:30 – 2:45	Break	
2:45 – 3:30	Highlights of recently-published research relevant to Gulf War veterans' illnesses	Dr. Lea Steele
3:30 – 4:15	Tissue banking resources and requirements at the Department of Veterans Affairs	Dr. Timothy O'Leary, VA Office of Research and Development
4:15 – 4:30	Discussion	
4:30 – 5:00	Public comment period	
5:00	Adjourn for the day	

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

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

Wednesday, September 21, 2005

8:00 – 8:30	Informal gathering, coffee	
8:30	Meeting called to order	Mr. Jim Binns, Chairman
8:30 – 10:00	VA Office of Research and Development update on Gulf War illness-related research activities	Dr. Joel Kupersmith, VA Office of Research and Development
10:00 – 10:30	Committee discussion with Department of Veterans Affairs Secretary James Nicholson	
10:30 – 10:45	Break	
10:45 – 11:30	Preliminary findings on multisymptom illnesses and treatments from VA's Longitudinal Study of Gulf War-era Veterans	Dr. Han Kang VA Washington, DC
11:30 – 12:00	Discussion	
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	

Dr. Beatrice Golomb, Committee member, was not able to be present for this meeting. Dr. William Meggs, Committee member, was not able to be present for the September 19, 2005, proceedings.

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 8:34 a.m.

Chairman Binns thanked the Committee members, speakers and public for attending the meeting. He introduced Dr. William Goldberg, PhD, the new portfolio manager for Gulf War illnesses research in the Department of Veterans Affairs' (VA) Office of Research and Development (ORD).

Chairman Binns stated that he wished to encourage discussion of the research to be presented, but asked that public comments be held until the scheduled time unless he specially opened the floor to discussion.

Chairman Binns expressed his pleasure that the meeting would include a presentation by and discussion with Dr. Joel Kupersmith, MD, the new Chief Research and Development Officer (CRADO) for VA. He indicated that he also was very pleased that VA Secretary Jim Nicholson would be participating. However, he expressed deep concern about other developments in VA Gulf War illnesses research since the Committee's April 2005 meeting. He stated that VA was lagging far behind in honoring commitments made by former Secretary Principi in November 2004, which were a response to the Committee's 2004 report.

Chairman Binns noted that the treatment development center research funding announcement (RFA), which was the centerpiece of those commitments, was still under review in draft form. He informed the Committee that Drs. Goldberg and Kupersmith were engaged in discussions with Dr. Steele and himself about the matter. He acknowledged that they had inherited a situation where the topic had not been advanced under previous leadership, but noted that it was clear that the treatment development center RFA would not even be issued in Fiscal Year (FY) 2005, let alone awarded and funded.

Chairman Binns next addressed the status of the general Gulf War illnesses RFA. This RFA was issued in April 2005 and proposals were received in June 2005. He noted, however, that the two merit review panels had only recently been named. The first review panel met on Friday, September 16, 2005, and a second panel was scheduled to meet on Friday, September 30, 2005. As with the treatment development center RFA, he noted that these proposals would not be funded in FY2005.

With respect to the review panelist selection process, Chairman Binns found it equally disturbing that the panel for the first merit review session did not contain a single scientist from a list of names suggested by the Committee. He explained that the Committee had prepared and submitted a list of over 50 suggested scientists' names to ORD in February 2005. He pointed out that a major problem in Gulf War illnesses research at VA had been that past review panels had not contained scientists with sufficient expertise in Gulf War illnesses and related areas. He noted that Dr. Steele had recently been appointed to the second review panel, but that the names of the other scientists were not known by the Committee at that time.

Chairman Binns expressed his concern about three of four new Institute of Medicine (IOM) studies initiated by VA in Fall 2004, which only came to public light when the IOM panels convened in Spring 2005. He stated that these studies were not initiated by ORD, but another part of VA, the Environmental Agents Service (EAS), directed by Dr. Mark Brown. He noted that the EAS is responsible for several

other Gulf War illnesses-related functions, including the War-Related Illness and Injury Study Centers (WRIISCs) and the Gulf War Review newsletter.

Chairman Binns stated that the Committee would normally welcome the involvement of IOM and the distinguished scientists and what that they could bring to bear in analyzing Gulf War illnesses research. He noted that it was a Spring 2005 IOM/VA study that identified the increased levels of brain cancer deaths in soldiers exposed to the Khamisiyah plume. He expressed concern, however, that the three new IOM studies were very limited in both the questions to be addressed and the materials eligible for review. He noted that the IOM panels would not consider animal studies, even though they were dealing with many topics that could only be ethically researched in animals. He also noted that federal research efforts had been focused on these animal studies. He stated that these IOM studies appeared to be a step backward to the era when the government was designing research studies for the purpose of suggesting that no problem existed, rather than trying to find answers for the problem. He indicated that he had expressed these concerns to Secretary Nicholson, along with a request for a complete review and reconsideration.

Chairman Binns also expressed concern that no new members had been appointed to the Committee in 2005, nor had sitting members been reappointed at the required time.

Chairman Binns expressed his belief that the work of the Committee continues to be important. He stated that when the official channels were not working, the Committee was there to point out the problems. When new research was not being pursued, the Committee was there to point the way. He noted again that he had expressed these concerns to Secretary Nicholson, in person, the previous week. He indicated that he looked forward to the day when the Committee's relationship with VA staff could be wholly collegial and mutually supportive. He stated that this would be a much more comfortable role, and have a much more productive outcome for ill Gulf War veterans. Meanwhile, he stated that the Committee was fulfilling an important function, and encouraged Committee members to voice their perspectives to VA staff and leadership.

Chairman Binns introduced Dr. Lea Steele, the Committee's Scientific Director.

Before beginning her presentation, Dr. Steele asked that all present use a microphone when they spoke, in the interest of clarity and for recording purposes. She noted that there was a literature table in the back, which contained agendas and selected journal articles pertaining to the day's presentations. She introduced Laura Palmer and Barbara LaClair, Committee staff.

Exposures and Gulf War Illnesses

Lea Steele, PhD
Scientific Director, RAC-GWVI

Dr. Steele gave an overview of exposures examined by the Committee over the past two years (2004-2005), and outlined the next steps facing the Committee in examining the data, weighing the evidence, and identifying research needs and priorities. (See Appendix A – Presentation 1.)

What Do We Know About Oil Well Fires and the Health of Gulf War Veterans? Overview and Review

Lea Steele, PhD
Scientific Director, RAC-GWVI

Dr. Steele gave an overview of the information previously considered by the Committee with regards to the 1991 Kuwaiti oil well fires, along with an overview of the epidemiological findings relating these fires to the health conditions of Gulf War veterans. (See Appendix A – Presentation 2.)

Dr. Steele introduced Dr. Gary Friedman, a pulmonologist with the Texas Lung Institute in Houston, TX. Dr. Steele explained that Dr. Friedman had evaluated U.S. civilian firefighters contracted to extinguish the Kuwaiti oil well fires in 1991.

Medical Outcomes of Oil Well Firefighters – Kuwait

Gary Friedman, MD
Texas Lung Institute, Houston, TX

Dr. Friedman provided the Committee with his observations regarding the health of civilian firefighters sent to the Gulf in 1991. (See Appendix A – Presentation 3.) (Note: Blank slides contained color field and aerial photos that were not transferable to black and white.)

Dr. Friedman noted that the civilian firefighters did not receive anthrax vaccine, nor were they known to be exposed to neurotoxins, such as sarin. He stated that these firefighters were the closest to a "pure" control cohort available in an uncontrolled setting.

Dr. Robert Haley agreed that the neurological aspects of Gulf War syndrome were not related to oil well fires. He noted, however, that there was some epidemiological evidence showing an increase in veterans being hospitalized for respiratory problems in the year following the war. He asked Dr. Friedman if a possible sequela of the oil well fires might have been obstruction of airways, exacerbation of pre-existing asthma, etc. He also asked whether this cadre of firefighters might have already purged out sensitive individuals through self-selection, removing "the folks who just couldn't take it," and whether it was possible that a portion of the troops who weren't purged prior to deployment might have experienced reactions to oil well fires.

Dr. Friedman acknowledged that there was a natural selection for the "healthy worker" among the civilian firefighters. He stated that individuals with reactive airway disease or asthmatic issues probably wouldn't be able to survive these working conditions and could not last long in this career field. He also noted that these firefighters had a "fighter pilot" mentality and may not report health problems. With regards to the increased hospitalization for respiratory problems, he stated that there were other possible exposures that could have been responsible, e.g., sand, kerosene, diesel fuel, munitions combustion products, etc. Oil well fire smoke might have contributed to the initial respiratory problems, along with these other exposures. However, he didn't see the oil well fire smoke causing long-term problems by itself.

Dr. Jack Melling asked whether it was possible to go back to the companies who employed these firefighters to see if they have a significant employee turnover in the first 1-3 years of employment. He stated that if the answer was "no," then these individuals would not be physiologically atypical. Dr. Friedman stated that this was an excellent idea, and would look into it. He noted that the average experience for the civilian firefighters was ten years, and that he was not aware of any rookie firefighters being deployed. It was noted that this might have resulted in a "superhealthy worker" effect.

Ms. Marguerite Knox asked for confirmation that these firefighters had pulmonary function tests pre- and post-deployment and that the results showed no changes. Dr. Friedman confirmed this. Ms. Knox compared these individuals to smokers who continue to smoke and exhibited no effects. Dr. Friedman noted that these firefighters were in theater for eight months, and that this was a short period of time to see lung function change. He acknowledged that some of these firefighters might have unreported problems now, but additional fire exposures over the intervening years would have to be considered in the equation.

Mr. Steve Robinson asked how many of the civilian firefighters were smokers. Dr. Friedman stated that there was one smoker out of fourteen firefighters in Dr. Etzel's study. He noted, however, that about 30% of the civilian firefighters were smokers.

Mr. Robinson noted, based on evidence presented at a recent conference in New York City, that there appeared to be an effect among Special Forces soldiers, a self-selected group, where they have resilience to Post Traumatic Stress Disorder (PTSD). He pondered whether this was occurring with this group of individuals, who apparently were completely unaffected by the fires. Dr. Friedman stated that none of these men sought medical attention following deployment or filed worker compensation claims. He noted that one company (Adair Company) had been sold in 1994. These workers dispersed, with many moving to another firm (Boots & Coots).

Mr. Robinson asked if Dr. Friedman's recent follow-up had been a verbal discussion with Boots & Coots, or whether he had reviewed medical records. Dr. Friedman stated it was a verbal discussion with the company's safety and health officers. The response, which he believed was candid, was that there were no problems to report. Mr. Robinson asked how the health of these firefighters compared with domestic/residential firefighters. Dr. Friedman replied that there were study cohorts that showed some minor respiratory problems. However, in industrial settings, these problems weren't seen.

Dr. Steele asked whether oil refinery workers exposed to petroleum fires exhibited any symptom-complex health problems. Dr. Friedman stated that, after looking at thousands of these employees, he hadn't seen these problems. However, these examinations were focused on respiratory issues, and the symptoms might have been overlooked before 1992 or 1993. Based upon his observations since then, he didn't believe that this was an issue in this group.

Mr. Robinson agreed that oil well fires did not cause Gulf War illnesses, but may have resulted in respiratory problems in some veterans. He asked Dr. Friedman if he concurred. Dr. Friedman agreed, and noted that some troops deployed into the oil fields could have experienced acute respiratory symptoms.

Dr. Haley asked Dr. Friedman to comment, for the record, on the possible mechanism by which oil well fires, sand, etc., might cause reactive airway disease. Dr. Friedman stated that reactive airway disease was an asthma-like disorder and could result from a single high-level inhalation exposure. He stated that, based on the reports from the Gulf at the time, there didn't appear to be high concentrations of the substances known to cause reactive airway disease.

Dr. Haley asked when the air pollutant monitoring occurred during the Gulf War. Mr. Robinson stated that it began in May 1991. Dr. Haley recalled that previous speakers had presented information that wind patterns had changed significantly between February 1991 and May 1991. Mr. Robinson noted that most of the sampling stations, which were located in Kuwait, were out of the oil well fire smoke plumes. He noted that the investigators believed this was where the majority of troops were located. Mr. Robinson

noted, as Mr. Joel Graves and other veterans had, that there were troops directly within the plumes for extended periods of time.

Mr. Robinson asked if there were any studies that looked at health effects of inhaling sand less than 10 microns in combination with volatile organic compounds (VOCs). Dr. Friedman stated that the RAND report had found 22% of the particulate concentration to be combustion product, with the rest being fine sand. He noted that the health effects of this exposure hadn't been examined in the report.

Chairman Binns asked Dr. Friedman if he had seen patients in his clinical practice with the type of multi-symptom conditions typical of Gulf War illnesses, and whether they had been associated with any particular type of exposures. Dr. Friedman stated that he had seen well-defined, long-term exposures to high levels of solvents or lead cause similar neurotoxic effects in occupational medicine patients.

Dr. Francis O'Donnell, a Department of Defense contractor, asked Dr. Friedman whether environmental sampling had been conducted by the firefighting companies in the areas where their civilian firefighters worked. Dr. Friedman stated that he was not aware of any such sampling.

Dr. Glen Ritchie, a meeting speaker, asked Dr. Friedman the following hypothetical question: What would be the health outcome of placing military personnel with no firefighting experience in this environment (1991 Gulf theater) for 10-12 hours-a-day, 7 day-a-week, for 90 days, with no respirators or protective gear. Dr. Friedman agreed there may be a natural selection among these individuals, and some wouldn't be able to handle the environmental conditions irrespective of the fires. He thought that the oil well fire smoke may just exacerbate the problem for some. Drs. Friedman and Ritchie commented that they personally would have difficulties in this environment. Dr. Ritchie noted that these military personnel already would fall into a "healthy worker" category but that the civilian firefighters represent the healthiest of the healthy, and really did not provide a representative control group. Dr. Friedman noted that studies looking at health risks from Kuwaiti oil well fires made their assessments based on air quality standards set by EPA, which were overly conservative and set to protect the health of infants, children, and the elderly. He observed that, in considering the health effects of oil well fires, it was important to consider both the health of the exposed and the measured levels of exposure. Dr. Steele noted that the measurements were not taken until after the height of the oil well fire exposures. Mr. Robinson added that, in one report, these later measurements had indicated that exposures were similar to those in major U.S. cities, such as New York City.

Ms. Denise Nichols, a Gulf War veteran, commented that an early IOM report had described elevated lead levels among some Gulf War veterans. Dr. Steele stated that these were autopsy results showing elevated lead levels in a small number of veterans

Chairman Binns asked whether there were other examples of studies that could be done to address the question of the health effects of oil well fires. Dr. Steele stated that it would be informative to look at the health status of other groups in the Gulf region at that time. She noted a recently published study regarding the health of Saudi Arabian National Guard members. These researchers had found no increase in hospitalizations, but didn't examine multisymptom illnesses. Dr. Steele stated that were studies looking at hospitalization rates among Kuwaitis in the periods before and after the Gulf War. In addition to these clinical studies, a new study looking at the health and mortality of Kuwaitis was being conducted by the Harvard School of Public Health, with preliminary findings indicating a 20%-30% higher mortality rate among Kuwaitis who remained in the country during the war, compared to those who left the area. She indicated that the investigators were currently assessing what might account for this increase, and that they planned to conduct future studies, which included health of younger Kuwaitis and prevalence of multisymptom illnesses.

Dr. Mark Witten, a meeting speaker, stated that he had conducted, on behalf of the United States Geological Survey (USGS), Type-2 cell culture studies with World Trade Center dust. He stated that they had found differences in the cytokine production of the individual cell cultures. He was waiting for the USGS to reveal which samples were controls. He stated that he had also published research which found firefighters in Arizona (Phoenix and Tucson), following fire recharge visits (usually without their protective gear), exhibited a significant decrease in interleukin 10 production. He agreed that the fires didn't cause health chronic problems, but there might be transient changes in some cell-mediated immune processes. He also agreed that these firefighters represented a "superhealthy" group which could withstand long-term exposure to this type of hazard. Chairman Binns noted that the World Trade Center dust might contain materials that were not present in the Gulf. Dr. Witten acknowledged this and indicated that his presentation later in the day would show that different particulate types/compounds produced different responses in the lung.

Dr. Steele mentioned that other groups who might serve as "pseudo controls" for selected Gulf War exposures would be military personnel from other countries who served in the Gulf War and that these groups would be considered in more detail at the next Committee meeting,

Chairman Binns thanked Dr. Friedman.

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

The meeting reconvened at 10:21 a.m.

Fuel Combustion Products, Particulates: Exposures and Epidemiologic Findings in Gulf War Veterans

Lea Steele, PhD
Scientific Director, RAC-GWVI

Dr. Steele gave an overview of the various fuel combustion products and particulates found in the Gulf theater and the epidemiologic findings regarding these exposures in relationship to ill Gulf War veterans. (See Appendix A - Presentation 4.)

Particulate Matter and Neurogenic Inflammation…Oxidative Stress-Mediated Toxicity

Bellina Veronesi, PhD
Neurotoxicologist, Neurotoxicology Division, United States Environmental Protection Agency
Research Triangle Park, NC

Dr. Steele introduced Dr. Veronesi.

Dr. Veronesi gave a presentation concerning the relationship between particulates/environmental exposures and oxidative stress, and how this might pertain to the understanding of Gulf War illnesses. (See Appendix A - Presentation 5.)

Mr. Robinson noted Dr. Veronesi's statement about seeing a blending of neurological disorders in her research. He stated that this also appeared to be the problem with neurodegenerative disorders affecting Gulf War veterans. He stated that their illnesses defied the traditional diagnoses and were considered MS-like, ALS-like, etc. He asked about the timing of brain sample collection, i.e., how soon after death

should samples be collected for the type of studies Dr. Veronesi was doing. Dr. Veronesi stated that her sample animals were not perfused with special fixatives, which worked well, and shipped in formaldehyde, which would not fix the tissue "too much." She stated that the brains were probably collected no more than 10-15 minutes after death. Mr. Robinson stated that one of the problems in this area of research was the failure to collect substantive evidence, e.g., tissue samples. He stated that several ill Gulf War veterans were interested in donating their brains for research, believing that this would provide evidence relating to overlapping neurodegenerative disorders. Dr. Veronesi stated that collecting clinical information probably would be a better approach. She stated that all of the populations she referred to earlier had cognitive and fine motor skills problems, which "fall out" with Parkinson's disease. She suspected that all of the neural populations were affected, but for some, motor neurons were specifically affected. She stated that there would be likely a mix within the Gulf War population of individuals affected by neurodegenerative diseases, with some due to service in the Gulf War and other environmental exposures and others due to aging.

Dr. Haley noted that, from a clinical viewpoint, the chronic multisymptom illnesses experienced by Gulf War veterans seem to wax and wane over a period of time. He wondered if this might suggest a periodic brain cytokine/inflammatory exacerbation. He stated that Dr. Veronesi's study approach was very provocative, and asked her to speculate what type of brain cell injury back in 1991 might produce a long-term illness with periodic swings of cytokine production and inflammatory conditions. Dr. Veronesi stated this was a good question, and that the answer could relate to innate immunity. She stated that in situations where the inflammation was steady and sustained in the periphery, the cytokines being produced could get through the blood-brain barrier, resulting in neuropathology. She indicated that microglia could be pushed "over the edge" so that they were always active and that that there were some insults from which the microglia could not recover. She noted that one of the discoveries in Parkinson's disease research was that activated microglia resulted in scarring twenty years later. She stated that there was neurogenetic information that could be used to explain Gulf War illnesses, including the findings regarding occupational pesticide exposure in farmers and their rates for Parkinson's disease. Dr. Haley asked Dr. Veronesi what her study approach would be if she had a bank of Gulf War veterans' brains. She stated that there were histochemical stains to look for microglia scarring.

Dr. Steele asked Dr. Veronesi to speculate about a situation like the Gulf War, where instead of accumulating toxins over time, individuals were exposed to several toxins in a brief time and whether there might be a synergistic effect. Dr. Veronesi pointed out that the vanilloid receptor (VR) could be stimulated by various triggers, including VOCs, acid pH, etc. With so many different types of chemical insults, the common link could be the vanilloid receptor. In addition, she noted that there was a parallel production of free radicals. She stated that this was a mixed bag, and she was sympathetic to the challenges facing Gulf War researchers looking at the situation after the fact. However, researchers should be able to tease out the problems, one agent at a time, since information was known about the pathways involved. She stated that, in combination, the effects could only be exacerbated.

Dr. Haley asked Dr. Veronesi to explain the microglia response process. Dr. Veronesi stated that the microglia released cytokines, along with free radicals which act in its microenvironment. She also noted that microglia were disproportionally distributed in the brain, with most being found in the hippocampus, substantia nigra, and spinal cord. She also noted that free radicals are very damaging, destroying cell membranes, proteins, etc. She stated that her research showed that this type of damage could occur in the brain, initiated years before and perhaps in combination with multiple exposures.

Chairman Binns asked Dr. Veronesi if there were any implications for therapies, other than avoiding further toxic exposures. Dr. Veronesi stated that the individuals could be eating as many anti-oxidants as possible, along with mega-doses of vitamins C and E.

Chairman Binns inquired as to whether organophosphates simply affected the body at the time of exposure, or were stored with continuing effects. Dr. Veronesi stated that OP had long-lasting effects, but much of the current research was focused on cholinesterase inhibition because it was easy to examine. She stated that there was research that suggested organophosphates were retained in the body, but whether organophosphates were retained in the brain was a question for pharmacokinetic researchers.

Chairman Binns asked Dr. Veronesi for her thoughts on future research in this area. She indicated that she hadn't thought about this in detail, but perhaps one should focus on the increased rate of Amyotrophic Lateral Sclerosis (ALS) in young Gulf War veterans.

Chairman Binns opened the discussion for public questions.

Dr Allen Fienberg, an audience member who is with Intracellular Therapies, Inc., asked two questions: (1) how might other vanilloid receptors play a role in this process, and (2) whether any human genetic association studies had been conducted. Dr. Veronesi stated that the vanilloid receptors were sensitive to very delicate changes in temperature, etc. She stated that the VR1 receptor was very sensitive to acidity. She noted that the process was very complicated, and they had approached it by looking at proton-charge triggers. She stated her research was starting to show that microglia have VR1 receptors and are sensitive to electrostatic charge, creating inflammation. She indicated that her research was focused on VR1 receptors and couldn't respond about the other vanilloid receptors.

Ms. Nichols commented that Gulf War veterans were dying, and that there needed to be a protocol so that families could donate these veterans' brains for research.

Chairman Binns thanked Dr. Veronesi.

The meeting adjourned at 12:20 p.m. for lunch.

The meeting reconvened at 1:20 p.m.

Solvent Exposures in the Gulf War

Lea Steele, PhD
Scientific Director, RAC-GWVI

Dr. Steele gave an overview of solvents exposures during the Gulf War, IOM's review of the possible health effects of these exposures, and the epidemiologic findings pertaining to Gulf War veterans' exposures to these solvents. (See Appendix A – Presentation 6.)

Dr. Melling asked if there was evidence that Gulf War veterans were exposed to more or different solvents than expected in regular military life. Dr. Steele stated that, for the most part, the solvents used were similar to those used in non-deployed areas. However, she noted a couple of exceptions, including CARC paint and decontamination solvents. She also noted that there was the issue of differing effects resulting from solvent exposure when combined with other Gulf War exposures. She stated that JP-8 jet fuel, for example, may affect an individual one way as a single exposure, but affect him or her differently when combined when other exposures.

Fuel Exposures of U.S. Military During the Persian Gulf War

Barbara J. LaClair, MHA
Research Health Scientist, RAC-GWVI

Barbara LaClair gave an overview of the various fuels, including JP-8 jet fuel, used during the Gulf War, the possible health effects of exposure to these fuels, and the epidemiologic findings pertaining to Gulf War veterans' exposures to these fuels. (See Appendix A – Presentation 7.)

Possible Role of Hydrocarbon Fuel Exposures on Development of Gulf War Illnesses

Glenn Ritchie, PhD
Group Leader, CNS Safety Pharmacology
Battelle, Columbus, OH

Dr. Steele introduced Dr. Ritchie.

Dr. Ritchie gave a presentation on the adverse effects of jet fuel exposures, with a particular focus on effects on the central nervous system. This included information on how repeated hydrocarbon exposures might synergistically increase adverse effects of exposures to other toxicants in contributing to Gulf War illnesses. (See Appendix A – Presentation 8.)

In response to Dr. Ritchie's mention of acute lymphocytic leukemia cases in Fallon, Nevada, Dr. Steele commented that she had received anecdotal reports of three cases of this cancer among Gulf War veterans in one fueling unit. Dr. Ritchie said that a thorough investigation in Kuwait was needed to examine blood cancer prevalence rates, as Kuwaitis had experienced some of the same exposures as Gulf War veterans. Dr. Mark Witten stated that he had learned, through contacts, that there was a large childhood leukemia cluster in Basra, Iraq. Dr. Steele noted, though, that alarms had not been raised thus far concerning increased cancer mortality rates, aside from brain cancer, in Gulf War veterans. Dr. Ritchie noted that the increased cancer rates were being seen in the children, not adults, of Fallon, NV and Sierra Viesta, AZ. Dr. Witten stated that a house-to-house survey in Fallon revealed 18 adults, primarily women, with various forms of brain cancer, with three additional cases reported since December 2004. Dr. Steele asked if symptoms were evaluated in populations with these exposures. Dr. Witten stated that there were anecdotal reports that there was an increased rate of autoimmune disease among town residents.

Dr. Ritchie stated that he wasn't implying that JP-8 jet fuel directly induced the health effects seen in Fallon/Sierra Vista. He stated that there was something unique about this environment and specific toxicants that perhaps interacted with JP-8 through the mechanisms discussed in his presentation.

Dr. Melling asked if the fuel usage in the Bosnian campaign was similar that that used in the Gulf War. Dr. Ritchie stated that, to a degree, it was. He stated that, due to different practices and environments, fuels weren't used to heat tents, for cleaning munitions or for sand suppression. He stated, however, that hydrocarbons may have been used for weed control. He noted that there were fewer vehicles and aircrafts as well.

Ms. Nichols asked if birth defects had been reported in Fallon. Dr. Witten stated that he wasn't aware of any increases, but that the focus of the investigation had been on cancers.

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

The meeting reconvened at 3:30 p.m.

Effect of JP-8 Jet Fuel Exposure on the Immune System and Lungs

Mark Witten, PhD
Lung Injury Laboratory
The University of Arizona College of Medicine, Tucson, AZ

Dr. Steele introduced Dr. Witten.

Dr. Witten provided a presentation on the effects of JP-8 jet fuel on the lungs and immune system (systemic and skin). (See Appendix A – Presentation 9.) He stated that research in which he was involved was showing that a Substance P analog might be able to "revive" immune cells adversely affected by acute radiation, formalin, respiratory viruses, etc. He indicated that they hoped it could be used as a dermal treatment for toxic exposures.

Dr. Steele asked how what is known about Gulf War illnesses might be integrated with the information presented by Drs. Ritchie, Witten and Veronesi. She noted that whereas jet fuel may be causing an inflammatory response with a dermal exposure, it may be immunosuppressive when inhaled. Dr. Witten commented that the pulmonary macrophages were designed to monitor the health of the lung, and that age was a factor in terms of immune responses in that the elderly and very young were more susceptible to the effects of exposure. He stated that the "take home message" was that age needed to be taken into account.

Dr. Veronesi asked if this Substance P analog was administered in ultra-low doses. Dr. Witten stated it really wasn't. He said that the levels used in the jet fuel studies to show this effect was about a billion times higher than the normal substance P levels in the lungs of rats.

Referring back to Dr. Veronesi's earlier presentation, Ms. Marguerite Knox noted Dr. Veronesi's description of microglia as scavengers and being of the same lineage as macrophages. She asked if microglia could be considered the "quarterback" of brain immunity in the same way as the alveolar pulmonary macrophages described by Dr. Witten for the lung, and whether microglia decrease in numbers with age. Dr. Veronesi stated that CNS microglia proliferate and go into marked neuropathological patterns called microglial scars or clusters. Dr. Witten noted that phagocytic cells had adapted to operate in virtually every major organ system in the body.

Dr. Steele asked about differences between scavenger cell activity in the brain and periphery. Dr. Veronesi replied that the brain normally wouldn't encounter xenobiotic substances. She stated that the brain was traditionally considered an immune-privileged organ, but the current environment was severely challenging human bodies. Dr. Ritchie stated that the microglia increase may be a response to brain damage. Dr. Veronesi stated that microglia also respond to insults themselves. She noted that she was working in isolated and pure immortalized microglia cultures.

Chairman Binns asked Dr. Witten for his suggestions on future research needed in this area. Dr. Witten suggested combination exposure studies, noting that his group had proposed a project to the U.S. Department of Defense (DoD) to study jet fuel, PB, DEET and trace amounts of sarin in controlled animal experiments. He also noted the need to identify a standardized Kuwaiti sand for these experiments. He stated that cell cultures could be used to rapidly screen toxic combinations, and then utilize animal models for those identified as most toxic.

Dr. Haley agreed with Dr. Witten's suggested approach of using cell culture, followed by animal models, and interpreting all of that in light of the epidemiology. He stated that an interesting phenomenon over the last couple of years is the tendency to ignore animal research in trying to answer questions about Gulf

War illnesses. He noted that there was significant toxicological animal research on sarin, pesticides and other agents but that IOM and other panels have taken the position recently to not consider this research in their analyses. Dr. Witten indicated he wasn't sure why they were taking this position. He stated that cell cultures can provide important information, but still leave questions. He said cell culture studies are valuable in keeping costs down and giving information on where more time and resources should be invested. However, without animal models, interactions can't be observed. Animal studies are more "real world."

Dr. Melling wondered if IOM ever talked with their U.S. Department of Food and Drug Administration (FDA) colleagues, who routinely require animal studies as part of the drug approval process. Dr. Haley stated that the IOM generally interprets animal studies along with human studies, but that VA had tied IOM's hands with the mission it gave them with the Gulf War projects.

Chairman Binns asked Dr. Witten if the Substance P analog drug being developed would have a therapeutic effect long after exposure, or only immediately following exposure. Dr. Witten stated that it works best after exposure, versus pre-exposure, but that he couldn't speak as to the timing after-the-fact. He stated that they were looking at whether it could stimulate the immune system. Chairman Binns asked if Dr. Witten had thoughts on directions for therapy in Gulf War veterans. Dr. Witten stated that the key thing was to develop a good standardized animal model, followed by drug screening and human clinical trials.

Ms. Knox asked if the drug might have the potential to reverse immune system damage. Dr. Witten stated that it was a possibility, and this may be due to increasing stem cell numbers. He reiterated that the research process should involve cell culture experiments with standardized toxins, followed by a standardized animal model and screening of potential drug candidates.

Dr. Veronesi stated that she understood OIF/OEF veterans were not developing the same illnesses as Gulf War veterans. She said the question then is what is different. Dr. Steele stated that question is being asked, and noted that problems were being seen in Gulf War veterans by this point after the war. Dr. Haley stated that when Gulf War troops were returning in April, May, and June 1991, veterans were lining up for health examinations, and that Walter Reed's medical consulting service was inundated. He said there were different categories of ill veterans, with one group being completely devastated. He stated that the initial focus for this group was leishmaniasis. He noted horrible medical problems in the current war, with a large number of traumatic injuries, deaths and post traumatic stress disorder (PTSD). He stated, however, that the multisymptom illnesses and cognitive problems did not seem to be developing.

Mr. Robinson noted that 1.4 million troops had served one, two, or three tours in the current Iraq war. Out of these individuals, 300,000 have been deactivated, with 180,000 being seen by the VA and tracked by ICD-9 codes. He stated that although DoD did not have comparative numbers of the discharge diagnosis for comparison with the presenting diagnosis at the VA, VA statistics did not reveal large numbers of veterans with neurological problems. He said that he had met some OIF/OEF veterans with Parkinson's-like tremor, and it was unclear if this was a PTSD reaction or related to Lariam usage. He stated that the illnesses from this war were better understood, and that DoD was doing a better job reducing the pesticide and hydrocarbon exposures. Dr. Haley noted that there also were no weapons of mass destruction (WMD), including nerve agents like sarin.

Mr. Graves stated that now, after reviewing the research related to all key exposures, the focus needed to be narrowed to those exposures which contributed to Gulf War illnesses. Chairman Binns noted that this was Dr. Steele's intention with the Committee's next report.

Chairman Binns thanked Dr. Witten.

Public Comment – Day 1

Chairman Binns opened the floor to public comment.

Ms. Nichols thanked the scientists present for their concern and interest in Gulf War veterans and their illnesses. She suggested an e-mail network of scientists to brainstorm in the same manner as the discussions at this meeting. She stated that blood cancers were being seen among Gulf War veterans in 1993-1994, and that data on these individuals should be collected. With regard to other populations for study, she noted that there has never been a true study with the U.S. Special Forces troops. She stated that veterans suffering from ALS should be followed for location and exposure pattern data. She also suggested that the research which emerged from the Bhopal chemical explosion be examined. She stated that cardiac and thyroid problems were developing in Gulf War veterans. She suggested that veterans be canvassed to find those who weren't being seen by the VA and their reasons for not seeking care there. She suggested that American Red Cross volunteers could help with this effort.

Chairman Binns thanked Dr. Steele for assembling the meeting. He stated there was a tremendous amount of scientific information that had already been uncovered, but because of the lack of time or established relationships, individual scientists were not fully aware of each other's respective work. He stated that meetings like this one created an opportunity to bring together strands of research that shed a great deal of light on the subject.

The meeting adjourned for the day at 4:45 p.m.

The meeting reconvened Tuesday, September 20, 2005, at 8:34 a.m.

Additional Exposures of Possible Concern in Relation to the Health of Gulf War Veterans

Lea Steele, PhD
Scientific Director, RAC-GWVI

Dr. Steele gave an overview of various Gulf War-related exposures not previously discussed by the Committee, focusing on microwaves/electromagnetic radiation, contaminated food and water, decontamination agents, and chemical agent resistant coating (CARC) paint. (See Appendix A – Presentation 10.)

Dr. Haley asked what the potential sources of microwave/electromagnetic radiation were. Dr. Steele stated that there was little information available about this. For example, she had received reports that some bases in theater were surrounded by microwave towers. Surveys that had asked questions about electromagnetic or microwave exposures had not elaborated further. Mr. Robinson stated that there were high-frequency satellite communication devices, fire finders, portable particle beam devices, high tension power lines, etc.

Mr. Robinson stated that the Office of the Special Assistant for Gulf War Illnesses (OSAGWI) had a database with information from veteran surveys regarding exposures. He stated it would be interesting to see what had been reported by veterans and in what numbers. Dr. Steele noted that some of OSAGWI's lead sheets were on the Internet, which included individuals' reports.

Dr. Haley stated that Dr. Han Kang's national survey was one of the most important and well-designed studies in the entire body of Gulf War veterans' illnesses' research. He noted that Dr. Kang had a risk factor table in his publications, which listed the most important risk factors. He expressed disappointment, however, that Dr. Kang's tables did not include odds ratios. He had calculated the odd ratios himself, finding all elevated with the highest ratio related to nerve gas exposure. He stated that there were eight epidemiologic studies that included a question about nerve gas, and every study showed nerve gas having the highest odds ratio/relative risk. He commented that epidemiologic studies shouldn't rely on unadjusted relative risks because there were many confounding factors. He suggested asking Dr. Kang, who was scheduled to speak the next day, about the risk factor odds ratios.

Dr. Meggs told the Committee that following an outbreak of food poisoning in Barcelona, Spain, there were affected individuals who had persistent problems. He stated that there was a possibility that a person reaches a threshold when it comes to multiple exposures, e.g., sarin and food poisoning, which pushes their inflammatory responses into overdrive. Dr. Haley stated that this was a good point, and suggested that Dr. Kang's data should provide information about the synergy among these risk factors.

Dr. Paul Levine, a meeting speaker who was also a coauthor with Dr. Kang on the study discussed, commented that a subgroup of deployed Gulf War veterans with an identified cluster of neurological symptoms was examined along with two control groups. He stated that they found that a lot of the illnesses and problems relating to these symptoms were due to comorbidities. He stated that there were no consistent differences between the veterans, except for electronystagmography (ENG) results in a few. He stated that Dr. Kang didn't feel that medical history interviews provided sufficiently reliable data for risk factors. He did note that receipt of multiple vaccinations, both in deployed and non-deployed veterans, stood out more than any environmental exposure. Dr. Haley asked if there were calculated odds ratios for the table in Dr. Kang's *Archives of Environmental Health* paper. Dr. Levine stated that he was involved in the clinical study and couldn't speak as to the analysis of the full group.

With respect to decontamination solutions, Dr. Susan Proctor, a meeting speaker, noted that ethylene glycomonomethylether (2ME) was similar to the deicing additives in jet fuel.

With respect to hydraulic fluid, Dr. Haley noted that there was an ongoing debate within the airline industry about hydraulic fluid exposures during flight. He discussed the history of various tri-cresyl phosphate exposures, including the Ginger Jake incident in the American South during the 1920's. Dr. Witten noted that hydraulic fluid exposure was a real problem on Navy submarines, while Dr. Meggs mentioned a recent incident at the Duke Medical Center.

Dr. Veronesi asked if residual delayed neuropathy was observed in individuals exposed to tri-cresyl phosphates. Dr. Haley stated that the Ginger Jake victims were followed for 30 years. He stated that they found that their peripheral neuropathy resolved over a period of six months to a year, but that a central lesion with spastic paralysis remained. With regards to Gulf War veterans, he stated that there was no evidence of either upper or lower motor neuron lesions. He stated that, in the Ginger Jake cases, the peripheral nerve lesion did repair itself, but the central lesion didn't. He speculated that, if there was repetitive low-level organophosphate exposure, a mild central and peripheral neuropathy might develop. However, because the peripheral damage was so mild, it might not have been noticed before it healed, leaving the central neuropathy undetected. Dr. Veronesi stated that she had worked on a project that studied multiple, low-level exposures to organophosphates and found that it helped nerves regenerate. She indicated that they were not sure why this had happened. Dr. Haley asked her what was known about the central neuropathy in these animals. Dr. Veronesi stated that there was damage to the dorsal cord, but the animals didn't show dysfunction. Dr. Haley stated that this might be an area of interest because it is an important parallel to Gulf War illnesses. He noted that there was early speculation that this could be a

mild form of organophosphate-induced delayed neurotoxicity (OPIDN). However, after conducting peripheral nerve conduction studies, he stated there was no evidence that this was the case in Gulf War veterans.

Dr. Steele noted that there was one epidemiologic study (Spencer) that asked about hydraulic fluid exposure, finding an unadjusted elevated odd ratio of 2.45 for chronic multisymptom illness if they reported cleaning hydraulic tanks.

Mr. Robinson noted reports of industrial pollutants, such as hexavalent chromium, at Al Jubayl. He also mentioned the "loud noise event", where it was postulated to be a patrol boat attack with missiles. Dr. Haley mentioned the supposed Scud missile explosion at Al Jubayl on the night of January 20, 1991. He stated that this happened near the Seabee's camp. Mr. Robinson stated that the green cloud they reported was assumed to be left-over rocket fuel, not necessarily a chemical warfare agent.

Dr. Steele asked the Committee to think about additional research, if any, that should be pursued in these less documented or less researched areas. She noted that there should have been a cohort study of the 325th Maintenance Company following their excessive exposure to CARC paint. Mr. Robinson noted that VA had made a special exception to track the Seabees at Al-Jubayl, but hadn't with the 325th.

Spatial Analysis of 1991 Gulf War Troop Locations in Relationship with Post-War Health Symptom Reports Using GIS Techniques

Susan P. Proctor, DSc
Assistant Director, VA Boston Environmental Hazards Research Center
Research Associate Professor, Environmental Health, Boston University School of Public Health and Medicine

Dr. Steele introduced Dr. Proctor.

Dr. Proctor gave an overview of her Geographic Information Systems (GIS) research project looking at Gulf War troop locations in relationship to veterans' post-war health symptom reports. (See Appendix A – Presentation 11.)

Mr. Robinson asked if it was possible to take Dr. Proctor's data and self-reported information and match it with historic troop movements in determining chronic multisymptom illness occurrence. Dr. Proctor indicated that would be possible but noted that the project didn't necessarily need to use GIS analyses and could include data on individuals rather than units.

Dr. Haley stated that this was an important study, but that he hadn't seen it in PubMed. Dr. Proctor replied that she had published it in a GIS journal because she wanted the methodology known and considered. Dr. Haley noted that, based on his research, the 3rd week in January 1991 in northern Saudia Arabia was a "hit", that is an important time and location in the Gulf War. He stated that this was at the same time Czechoslavian teams detected sarin at King Khalid Military City (KKMC). He asked Dr. Proctor for her thoughts about this time period. Dr. Proctor stated that several things happened during that week. She stated that their group of study subjects was still in urban areas during that time, but none had been in Al-Jubayl.

Dr. Steele asked if there were Scud missiles reported at KKMC area during that time. Ms. Knox, who was stationed at KKMC January-May 1991, stated that 10 Scud missiles were reported going over KKMC. She asked if Dr. Proctor had looked at the correlation between chronic multisymptom illness

patients and VA compensation. Dr. Proctor stated that her study was based on veteran questionnaire responses at one point in time, and then applying the chronic multisymptom illness criteria to categorize them. Ms. Knox asked if there was a way to correlate the identified chronic multisymptom illness patients with VA benefit compensation. Dr. Proctor stated that there was, and that this was part of the Devens' studies. She stated that approximately 30%-40% of the veterans were on the Gulf War registry, and approximately 8%-9% were receiving compensation. Ms. Knox noted that KKMC was within the Khamisiyah plume area.

Dr. Steele asked Dr. Proctor what it meant that she had identified local hot spots but didn't see global clustering. Dr. Proctor stated that their first question, i.e., the global question, was looking at the whole region at a particular time, whereas their second question looked at each of the locations, drew a buffer area around them, and tested whether cases within that area were significantly elevated compared to the area around them. Dr. Steele asked Dr. Proctor if one normally expected clustering in hot spots, but lost the effect when the lens was zoomed out. She wondered if the small cohort size and Bonferroni corrections might have created a "power issue." Dr. Proctor stated that there were sample size issues when using the global approach. Dr. Steele asked if Dr. Proctor had any sense whether there was some nonsignificant indications of clustering. Dr. Proctor stated that, because of all the questions, they focused on the significant clustering.

Dr. Steele asked if Dr. Proctor had considered working with Dr. Kang's survey data to do a similar analysis. Dr. Proctor stated that she hadn't talked with them, but would be interested in doing such a study.

Dr. Proctor stated that her group was now looking at currently deployed soldiers, and had pre- and post-deployment information on over 1,000 personnel. This study includes in-person cognitive testing, location interviews and questionnaires.

She was also working on a retrospective case-control study, which looks at VA patients diagnosed with ALS and Parkinson's disease and whether there is any correlation between their illness and early military/occupational exposures. This study includes about 100 ALS patients, matched with 300 controls, and 400 Parkinson's disease patients, matched with 1200 controls, with a focus on individuals who were diagnosed between the ages of 30-60 years. It includes all eras of veterans and is not limited to Gulf War veterans. She stated that the research team was currently in the process of conducting case record reviews to confirm diagnoses.

Dr. Veronesi asked if the individuals classified as not having ALS or Parkinson's were being separated into an "other" group for nonspecific neurodegenerative conditions. Dr. Proctor stated that they hadn't determined this yet, and were just starting to see what sort of diagnoses they really had. She mentioned that she was also trying to start an occupational study looking at JP-8 jet fuel exposure in Air Force personnel.

Mr. Robinson asked, with regards to her study of the soldiers in the current war, how many individuals were involved and how many were still in Iraq. Dr. Proctor stated that there were about 1500 troops, primarily deployed in the second rotation. She stated that they will have data from comparison veterans who were not deployed, including a group who is now deployed. This group will have two pre-deployment base lines.

Mr. Robinson noted that the VA was tracking the ICD-9 codes and diagnoses of returning veterans from the current war. He asked what her group was seeing in terms of injuries and illnesses and whether they were seeing unknown problems. Dr. Proctor wasn't sure if she could really answer this question because

the post-deployment data was collected 40-45 days following their return. She stated that they were going to be doing a 10-month follow-up in garrison. She stated that, from their general tracking data right now, they were seeing a number of traumatic head injuries.

Dr. Steele asked if they were conducting neurocognitive and symptom assessment at the short-term (40-45 day) follow-up. Dr. Proctor stated that they hadn't analyzed the symptom data, but there didn't seem to be a lot of symptom reporting. She stated that they were still working on the neurocognitive results.

Following up on Dr. Veronesi's question, Dr. Steele asked if Dr. Proctor planned to include those individuals who didn't meet the case definition of ALS or Parkinson's in a "neurodegenerative" group. Dr. Proctor stated that she hadn't thought about doing this, but may now because of the numbers. Dr. Steele stated that many veterans are reporting ALS-like or Parkinson's-like conditions, and it could be important to look at these individuals.

Chairman Binns thanked Dr. Proctor.

The meeting adjourned for a break at 10:39 a.m.

The meeting reconvened at 10:59 a.m.

Acetylcholinesterase Activity in Gulf War Deployed and Era Veterans: September 2005 Update

Mihaela Aslan, PhD
Associate Director, Clinical Epidemiology Research Center, West Haven VA Medical Center, CT
Associate Research Scientist, Department of Internal Medicine, Yale University

Dr. Steele introduced Dr. Aslan.

Dr. Aslan provided the Committee with an interim report regarding her group's on-going study of acetylcholinesterase (AChE) and other enzyme levels in ill Gulf War veterans. (See Appendix A – Presentation 12.)

Dr. Meggs stated that the earlier discussions about this study suggested that AChE-R might be a biomarker for Gulf War illnesses, but that the results presented by Dr. Aslan suggested the opposite now. Dr. Haley stated that he wasn't sure this was necessarily the case, and asked to look at the slide with the Gulf War illness Definitions 1 and 2. Discussions, which included Dr. Peter Peduzzi, PhD, occurred as to the "healthy" and "ill" definitions used for GWI cases and noncases. Questions included whether the control group was "pure," that is, whether it included people with multisymptom illnesses or other conditions. Additional discussions focused on the study's original protocol as set by VA and the initial question and hypothesis posed by the Committee. It was noted that Dr. Soreq's initial data suggested that an elevated levels of AChE-R were associated with chronic symptoms following pesticide exposures, and so might be associated with Gulf War illness.

Dr. Veronesi stated that there was abundant literature on how cholineseterase activity reflects cognitive or mood disorders. She noted that serum cholinesterase was tricky to use as a biomarker because it recovers so fast. She stated that measuring AChE activity in the brain was more tedious but would be more valid. She also noted that peripheral activity doesn't measure central activity. Dr. Meggs explained that Dr. Soreq's work had shown that the ratio of AChE and AChE-R was altered following organophosphate exposures, and that was the basis for this study with Gulf War veterans.

Dr. Peduzzi noted that other analyses using these case definitions had been presented by Dr. Concanto previously, and asked why they had raised questions now. Dr. Haley and Dr. Steele indicated that the concerns related to the effect of the case definitions on the control groups had not been clear until Dr. Aslan's presentation. Chairman Binns stressed that the Yale/West Haven researchers were coping with a situation not of their making. He stated that this process began three years ago, when the Committee suggested and asked what was thought to be a simple question, i.e., compare AChE-R levels of ill Gulf War veterans and healthy controls and see if there was a difference. He stated that the concept was taken by VA ORD staff, and "tortured" into the study proposed to Yale/West Haven VA. He stated that he appreciated the work that this group had done, especially with the limited data available.

Dr. Peduzzi asked for direction from the Committee to address its concerns. Dr. Steele stated that she would follow-up with them on these matters.

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

The meeting reconvened at 1:07 p.m.

Mortality in US Army Gulf War Veterans Possibly Exposed to 1991 Khamisiyah Chemical Munitions Destruction

Tim A. Bullman, M.A.
Data Manager, Washington, DC, VA War-Related Injury and Illness Study Center

Mr. Bullman gave an overview of his group's findings relating to mortality rates, particularly due to brain cancer, among Gulf War veterans possibly exposed to sarin gas from the destruction of munitions at Khamisiyah. (See Appendix A – Presentation 13.)

Dr. Meggs inquired about the controversy surrounding the modeling of the Khamisiyah plume. Dr. Melling stated that GAO had reviewed DOD's plume modeling effort, and concluded that even the revised 2000 model was possibly an underestimate due to deficiencies in the modeling process. He stated it was interesting that Mr. Bullman's findings still showed an excess of brain cancers among "the exposed." He stated that one could postulate that the 100,000 troops identified in the DOD model might be the most highly exposed, although not everyone who was exposed. He suggested that future work look at a comparison of in-theater deployed vs. not-in-theater non-deployed. Mr. Bullman stated that this had been done, and they hadn't found an excess in brain cancers.

Mr. Robinson asked if Mr. Bullman had plotted the troop locations in relation to Khamisiyah. Mr. Bullman stated that they hadn't done this, but it was being considered for future research. He stated that they had looked at their military occupations, and there wasn't a difference between the two groups. The vast majority of both groups were support/truck drivers. The only difference seen between the two groups, based on the available data, was one group was considered "exposed" in relation to the Khamisiyah demolitions and the other wasn't.

Mr. Robinson noted Mr. Bullman's comment about there being no previous sarin studies showing a linkage with cancer. He stated that, even if there was a linkage, the IOM would not consider this data because it doesn't look at animal models in Gulf War veterans' studies. He asked if Mr. Bullman knew what the potential exposure was at Khamisiyah. Mr. Bullman stated that their data didn't address this.

Dr. Steele asked if Mr. Bullman had looked at neurological diseases in its review of the data. Mr. Bullman stated that they had and found that the mortalities between the groups were the same, except for brain cancer.

Dr. Haley stated that this was a landmark study, and the researchers should be congratulated for taking it on and following through. He agreed that it was critical in future research to use GIS plotting of these cases to see if there is a pattern. He noted that this information might help to determine, through back tracking, where the plume was. He noted that there also had been a lot of discussion about this paper, and noted the statement that sarin is not a known carcinogen. He asked if this had ever been tested, though. He stated that he had not been able to find a study where animals were exposed to sarin with the intention of following them long enough to detect cancer. He said most sarin studies were focused on immediate effects, mostly cholinesterase inhibition. He noted that this had shifted somewhat with more recent research looking at long-term effects of low-dose exposure. However, he couldn't find anyone who had studied whether sarin was a carcinogen, particularly for brain cancer.

Dr. Steele inquired about the known etiologic agents for the types of tumors identified in this study. Mr. Bullman stated that risk factors for brain cancer included petrochemicals and agrochemicals.

Dr. Melling noted Dr. Henderson's study, which found that low-dose sarin had immunosuppressive effects. He wondered if her observations might be one biologically plausible mechanism for Mr. Bullman's observation. Dr. Haley stated that this was an interesting idea. Dr. Steele stated that Dr. Henderson's group was interested in doing follow-up studies on immunosupression to see how long it lasted after low-level sarin exposure.

Ms. Knox noted that KKMC was in the initial 1997 cohort considered exposed to the Khamisiyah plume, but removed following the 2000 revision. She stated it will be interesting to see how Mr. Bullman's findings relate to this area.

Dr. Meggs inquired about the UN Special Commission reports of October 1991-May 1998 that were quoted in Mr. Bullman's *American Journal of Public Health* article. Mr. Bullman stated that these were available on the DeploymentLink website.

Dr. Steele asked about using this type of information in conjunction with data from the large national survey of Gulf War-era veterans. Mr. Bullman stated that group working on this project had wanted to look at the health care utilization of veterans after being notified of their potential exposure at Khamisiyah. Dr. Han Kang, a meeting speaker, stated that this study was currently being published. Dr. Steele asked if there was an effort to use these data (from the plume modeling and health survey) to see if there were symptom patterns related to Khamisiyah exposure. Dr. Kang stated that this research was in the process of being published too.

Mr. Robinson asked for clarification with regards to the brain cancer findings of the non-deployed vs. deployed. Mr. Bullman stated that, when looking at all Persian Gulf-era veterans combined, there was no increase in brain cancers compared to nondeployed. Dr. Haley commented that there was an old fallacy in Gulf War illness research of comparing the whole deployed population with the non-deployed population. He stated that the problem was there was only a small percentage of the deployed population affected. When these numbers are combined and compared, effects can be "washed out" or averaged out. He stated a better comparison would be the Khamisiyah exposed group to the whole non-deployed group. He recognized that comparing the deployed Khamisiyah exposed to the deployed non-exposed controlled for other deployment conditions.

Mr. Graves noted that Mr. Bullman's latency analysis divided the nine-year period into three groups. He stated that it would be interesting to capture the next three year period data, creating a 12-year study. Mr. Bullman said that they were continuing to follow this group, and it would be good to do this. Dr. Meggs commented that the follow-up to this study would be very important to see if the increase in brain cancer was or wasn't a statistical aberration.

Dr. Steele asked if they had compared the mean age at death from brain cancer in these veterans with the general population. Mr. Bullman stated that they had, but he didn't have that information with him. He offered to provide the Committee with this information following the meeting.

Chairman Binns opened the discussion for public questions.

Mr. Kirt Love, an audience member and Gulf War veteran, asked Mr. Bullman if they had studied the post-mortems and compiled data on the lung tissue of the veterans with brain cancer. Mr. Bullman stated that they had requested minimal records for review of the diagnosed cancers.

Mr. Love stated this precursor information might show whether these were primary brain cancers. Dr. Meggs stated that histopathology answered this question. He stated that he didn't believe there was one cancer that metasizes to the brain with the histopathology of a glioblastoma. Mr. Love stated that animals were euthanized before they reached term in these studies, so there were still questions. Dr. Steele noted that Mr. Bullman's group was working with mortality data and hadn't collected tissue samples.

Ms. Nichols suggested comparing this information with the areas in which depleted uranium was used. Mr. Robinson stated that the depleted uranium exposure maps would pretty much cover the same areas as the Khamisiyah plume map, but noted that the depleted uranium maps were even less reliable than the Khamisiyah maps.

Chairman Binns thanked Mr. Bullman.

Cancer Patterns in Gulf and Non-Gulf Veterans

Paul Levine, M.D.
Research Professor of Epidemiology and Biostatistics
Clinical Professor of Medicine
George Washington School of Public Health and Health Services

Dr. Steele introduced Dr. Levine.

Dr. Levine gave an overview of his group's research on the occurrence of cancer, by type, among Gulf War and non-Gulf War veterans using data from state cancer registries. (See Appendix A – Presentation 14. [NOTE: Preliminary analytic results in Dr. Levine's slide presentation are provided for update purposes only. Because these results are preliminary in nature, they are subject to change following additional data analyses.] This research included cancer among veterans in California, Texas, New York, Florida, Illinois, New Jersey, Maryland and Washington, DC.

Dr. Haley suggested that future studies include North Carolina because the largest concentration of Gulf War veterans lives there. This is followed by Texas and California. Dr. Levine indicated that this was planned, and that the first round of analyses had focused on the states with the largest general populations. Dr. Haley suggested merging in the Khamisiyah plume data into this study too. Dr. Levine invited his colleague, Dr. Heather Young, to comment on this. She stated that they had analyzed the Khamisiyah

data in relation to two states, Texas and Illinois, and found no significant associations. She stated that they didn't have this data for all of the study states at the start of the project. However, they have acquired this data and should be able analyze it at some point.

Dr. Haley noted that Dr. Levine's results suggesting an increase in brain cancer in Gulf War veterans correlated with Dr. Kang's and Mr. Bullman's findings. He noted, however, that the increase in testicular cancer might not have been observed in Dr. Kang's mortality study because most of these individuals are successfully treated and live.

Dr. Levine noted that the institutional review board application for the next round of the study had already been distributed. However, he indicated that, if the Committee believed a particular group, e.g., the 325th Maintenance Company, needed additional focus, they were willing to include it in future studies.
Dr. Levine noted that when studying cancer clusters, one needed to define the population before looking for individual cancer cases. He stated that the process should not be done in reverse. Dr. Steele thanked Drs. Levine and Young for their earlier assistance consulting with a veteran's physician and herself with regards to an unusual cancer exhibited in this particular veteran. They had been able to look at their data to see how many of these tumors had been reported in the deployed and nondeployed veterans. While they found that more tumors of the type in question had been reported in non-deployed veterans, she stated it had been helpful to the veteran's physician to find out whether there might have been an association with the veteran's deployment.

Ms. Knox thanked Dr. Levine for helping the Committee in its task of making recommendations to the VA and veterans. She stated that she was a medical officer in the National Guard, and knowing that testicular cancer was found at a higher rate indicates that these soldiers should be taught how to do testicular self-examinations.

Ms. Nichols asked why Oklahoma, Mississippi, Alabama, Louisiana and Kansas weren't being considered in this study. She noted that these states had a large number of veterans assigned to tanks and engineering. Dr. Levine stated that they had focused on states with gold or silver rated cancer registries. He stated that it didn't make sense to go after data unless it was of good quality.

Chairman Binns thanked Dr. Levine.

The meeting adjourned for a break at 2:24 p.m.

The meeting reconvened at 2:50 p.m.

Highlights of Recently Published Research

Lea Steele, PhD
Scientific Director, RAC-GWVI

Dr. Steele gave a brief review of recent Gulf War research, which included epidemiologic studies, health effects studies pertaining to Gulf War-related exposures, and treatment studies for multisymptom illnesses. (See Appendix A – Presentation 15.)

During the discussion of Dr. Eisen's paper and the issue of whether using the case definition of fibromyalgia and chronic fatigue syndrome adequately captured all Gulf War veterans with fatigue and musculoskeletal conditions, Mr. Kirt Love stated that, even though he qualified for a diagnosis of fibromyalgia, it was not listed in his VA medical record and was being ignored. Mr. Graves stated that he had visited his physician after the last Committee meeting, and had been told that he probably had fibromyaglia. However, the physician had no treatment, other than antidepressants, to provide for the condition.

During the discussion of Dr. McDiarmid's paper, Mr. Robinson noted that test methods to detect depleted uranium have been debated extensively. He stated that there was a movement among returning veterans to not have their urine screened by DOD or VA. He noted that several states have passed laws to have their National Guard units use testing laboratories located outside the United States, and were in the process of looking for ways to pay for this screening.

Discussion occurred about the VA's protocol for depleted uranium testing for returning veterans.

VA Tissue Banking

Timothy J. O'Leary, M.D., Ph.D.
Director, VA Biomedical Laboratory Research and Development Service
Acting Director, VA Clinical Science Research and Development Service

Dr. Steele introduced Dr. O'Leary.

Dr. O'Leary gave an overview of considerations related to tissue repositories at VA and establishing a Gulf War veterans' tissue bank. (See Appendix A – Presentation 16.)

Dr. Meggs commented that the solution for the Gulf War problem may lie in the remodeling of the brain, and that the answer may lie in the brain pathology. He stated that the only way to answer these types of questions was with autopsy studies. Dr. O'Leary agreed that a banking effort was important, but cautioned that one had think about what studies needed to be done so that the samples were processed in a manner which allowed useful results.

Mr. Robinson asked about the tissues currently possessed by VA for Vietnam and Gulf War veterans, in relationship to their exposures. Dr. O'Leary stated that he didn't have a complete systematic survey of VA tissue banks, but he didn't believe there was a specific VA tissue database aimed at this purpose. He stated that clinical records could be linked to archival specimens. Dr. Steele asked whether these archival specimens could be used considering the identification concerns raised in Dr. O'Leary's presentation. Dr. O'Leary stated that it was theoretically possible, but he wasn't sure about how to specifically approach it.

Dr. Steele asked if blood samples had been collected for the VA's ALS registry, and whether these samples could be used if a researcher had a study question concerning a genetic association with ALS in veterans, even if the veteran was deceased. Dr. Haley noted that the Belmont protocol had a fundamental

distinction between surgical and post-mortem specimens. Dr. O'Leary stated that there were few issues with specimens from deceased individuals under most of laws, except for HIPPA. He noted that these issues and concepts were still being sorted out. He stated that the conclusion of a conference committee, which he recently chaired, was that federal agencies needed to come together and develop a set of tissue banking guidelines which complied with common rules and current statutes. He also noted that genetic studies provide information on both the living and dead, and the general conclusion of the scientific community has been that next of kin consent is required.

Mr. Robinson noted that the VA had blood samples taken before the Gulf War (Task Force Ripper – Marine), but that no studies had been done using them. He asked if these samples were still available, and if so, if the Committee could be provided, mindful of HIPPA requirements, with information as to what samples were on file. He asked if information about the Armed Forces Institute of Pathology (AFIP) samples could be acquired too. Dr. O'Leary stated he didn't know enough about the Task Force Ripper specimen collection to give a meaningful answer. He said that he would be happy to research this matter though. With regard to the AFIP collection, he stated that it contained many types of specimens, but hadn't been collected in any epidemiologically-directed way. He said that DOD would have to speak as to what information it would provide about their collection.

Dr. Steele asked Dr. O'Leary if there was a listing of what tissue samples VA had on file. Dr. O'Leary stated that he was reviewing this information, and was looking at survey data collected in 2002. He stated that he intended to "get his arms around this problem" within the next month.

Chairman Binns noted that Dr. Paul Greengard had commented that "one good brain" could provide much needed information. He acknowledged that there were legal complexities that needed to be addressed. But, without jumping to the concept of a new facility at VA to collect brains from veterans, with long-term financial implications, he stated that there were two questions which needed to be answered. First, he asked if there might be "one good brain" within the current system preserved in a suitable format for study. Second, he asked if there was already a tissue bank, particularly a brain bank, that a Gulf War veteran could be directed to for donation of his/her organs.

Dr O'Leary stated that he believed there might be relevant brain specimens within the VA system. However, he wasn't optimistic that an "ideal" brain would currently be available in the VA system. He stated that ideal brain would be "fresh", i.e., harvested quickly following death after a short period on life support. He indicated that there was a facility at Washington University in St. Louis which did occasional tissue collection in this manner, but it wasn't the most common situation.

Mr. Robinson noted the VA's fourth mission in relation to the larger community and the potential for a chemical and biological weapons attack on U.S. soil. He stated that the VA might be called upon to conduct autopsies to discover different types of bacteriological or chemical warfare agent exposures. He commented that if the VA didn't have those capabilities now, it might need to consider it for homeland security. Dr. O'Leary stated that mass casualties were an important area, and that DOD had the lead on this matter if called upon by Homeland Security. He stated that this type of investigation took a forensics approach rather than a regular clinical approach. He stated that VA had little forensic capabilities. He stated that the forensic pathology community, while small, was aware of these concerns and had evaluated various scenarios.

Chairman Binns commented that the advantage that VA has with respect to this issue is that it is an extremely large HMO with a large number of ill Gulf War veterans. He suggested that VA could use its network to alert its clinicians to invite veteran patients and their families to consider donating their organs. Dr. O'Leary stated that this was an interesting suggestion. While he wasn't in a position to

commit to this course of action, he would be willing to recommend that the Department evaluate such a program. Dr. Steele asked if there was a precedent for this with any other diseases or situations. Dr. O'Leary stated that he wasn't aware of any. Dr. Steele asked if any current tissue collection efforts at VA involved a "SWAT team" approach to collecting samples from around the country. Dr. O'Leary was not aware of this approach being taken by any government or academic organization. He was aware of occasional partnerships between local or regional commercial and private organizations, but wasn't aware of any on a nationwide basis. He noted that there would be logistical concerns with respect to identifying donors and assuring sufficient supplies. He thought this was a possible approach, but was uncertain how it would ultimately work.

Dr. Steele asked if there was a precedent at VA of bringing tissue samples to a central repository from distant outlying regions. Dr. O'Leary stated that the typical situation was a location with a specific clinical program or a second opinion referral center. He stated that these submissions were made in a way where they were fed into a central location that operated synchronistically with the submitting institution.

Dr. Steele asked Dr. O'Leary if he could elaborate on the National Cancer Institute (NCI) collaborative oncology group mentioned in his presentation. He explained that there were many VA medical centers participating in cooperative trial programs with NCI. Most of these study groups maintained tissue banks, which were specific for the diagnosed tissue containing the cancer. These were collected to determine if the patient qualified for the study and were sent to a central coordinating center, which verified the diagnosis and then would bank the tissue. He stated that, while there was an agreement between VA and NCI for these banks, it was not a program with a lot of central management.

Dr. Steele asked whether making tissue samples stored at VA available to non-VA investigators could be a source of financial support for tissue storage expenses at VA. Dr. O'Leary stated that, in general, tissue banks have mixed models of support. They have some form of core support, but may collect fees for specimen preparation costs. He stated that there was no common support model and that the general philosophy was that fees should cover the actual expenses only, with no realized monetary profit from the tissue transfer.

Dr. Kang informed the Committee that CP458, or the National Gulf War Survey Stage 3, collected approximately 1000 blood samples from Gulf War veterans. He stated that these were sent to the Maverick VA Medical Center in Boston, MA. Dr. Steele stated that she knew field investigators who had been interested in accessing this resource, and asked how they might be able to do this. Dr. Kang stated that the investigator would need to join with a VA principal investigator, if they weren't already one, and submit a proposal to the Hines executive committee. Dr. O'Leary explained that Maverick was an epidemiology and clinical trials coordinating center. He stated that if someone does submit a proposal to this group, it would be good for his office to be contacted, too, so it could be responsive to the situation.

Chairman Binns opened the discussion for public questions.

Mr. Love raised the situation of a veteran in Michigan who wished to donate his brain, but that there was no VA funding for the autopsy. He also stated that AFIP was shutting down, and there were plans to build sample vaults at a new location on a military instillation. He noted that there was a time lag and problem trying to get a catalog database of these samples before the agency was dissolved. Dr. O'Leary stated that the situation with AFIP was complicated. He stated that any conclusion as to what would happen with the samples was premature. He stated that AFIP was originally placed on the "black list," but the "black list" had been morphing. With respect to the veteran who wished to donate his brain, Dr. O'Leary asked Mr. Love to provide him with more information so that he could explore the issue in more detail. Mr. Love pointed out that there was urgency to this situation, which Dr. O'Leary acknowledged.

Ms. Nichols stated that numerous veterans over the years have contacted her with questions as to how they could donate their organs. She stated that there has been no protocol for 15 years for accepting these donations. She expressed her anger at listening to a theoretical discussion when the focus should be what samples were currently available and what samples could be collected.

Chairman Binns thanked Dr. O'Leary. He commented that he understood and appreciated the complexities of working in government and large institutional medicine. He noted that taking a proactive stance on a matter which appears to a layman to be relatively straight-forward, i.e., establishing a protocol by which veterans could donate brains, would have a large impact on veterans' impressions as to the federal government's efforts in this area. He encouraged and appreciated Dr. O'Leary's willingness to explore this matter.

Public Comment – Day 2

Ms. Venus-Val Hammack, an Army Gulf War veteran, spoke to the Committee. She indicated that she would have limited comments at this time but would be submitting written comments following the meeting. She did note, however, that VA ORD seemed to be responding very slowly to the Committee's requests and suggestions.

Chairman Binns thanked Ms. Hammack.

Ms. Nichols spoke to the Committee. She stated that she was upset after reviewing information about VA ORD's funding of Gulf War research. She stated this wasn't the Committee's fault, and encouraged it to continue "staying on top" of VA ORD. She stated that research funding issues was one thing, but the disruption that happens when VA Secretaries change is another thing. She stated that the Committee needed to issue an annual (2005) report, listing the problems encountered over the past year that had hampered productive efforts. She stressed that the problems raised during the Committee's meetings needed to be made public. She implored the Committee to remember it was established by Gulf War veterans' efforts, and they were counting on it to take the "lead" for them.

Chairman Binns thanked Ms. Nichols.

Mr. Wesley Crawford, an audience member and Navy Gulf War veteran, spoke to the Committee. (Mr. Crawford submitted a two-page summary of his comments. This can be found in Appendix B – Public Submission 1.) He informed the Committee that he was suffering from a variety of symptoms, discussed the various exposures he experienced in the Gulf War theater, and outlined six specific requests and recommendations. He concluded by saying that veterans were continuing to be told that they don't have this illness even with documentation and proof. This illness is not limited to veterans who were in the desert. He thanked those within VA, independent researchers and the members of the Committee who were working hard to help the veterans with this illness.

Mr. Robinson inquired about Mr. Crawford's specific service. He informed Mr. Crawford that he was eligible to be seen at the War-Related Illness and Injury Study Center (WRIISC), whose office was located on the 6th floor of the building. He offered to escort Mr. Crawford up to their office after the meeting so that he could discuss his options with them. Mr. Robinson thanked Mr. Crawford for his comments and asked to speak with him after the meeting. Mr. Robinson explained that he had found out, in his work with John Richardson and others, that individuals with the Glucose 6-Phosphate Dehydrogenase (G6-PD) deficiency should not receive the anthrax vaccine.

Chairman Binns thanked Mr. Crawford for coming to the meeting.

Mr. Kirt Love, with the Desert Storm Battle Registry, addressed the Committee. He provided a presentation showing his research on the Khamisiyah plume modeling, particularly focused on weather data, from March 10, 1991. He indicated that satellite imagery for that date in 2005 contradicted conclusions from DOD's official plume modeling of the Khamisiyah demolitions. His presentation is summarized in Appendix B – Public Submission 2 .

Mr. Robinson stated that the Government Accountability Office (GAO) agreed with Mr. Love that DOD's modeling effort was flawed. Mr. Robinson noted that the direction of the sun was incorrect in DOD's first model, and the third model miscalculated the percent strength of sarin located at Khamiyisah. He stated that Mr. Love was documenting these inconsistencies with great pictures.

Mr. Love stated that the U.K. Ministry of Defence (MoD) had also confirmed GAO's findings. He noted that all his information and photographs were taken from government websites. Mr. Robinson stated that the CIA information had been available since April 2002 when it posted its assessment of the demolition operations in Iraq. He stated that the images were only posted recently. Mr. Love stated that, as of February 2005, Iraq was no longer considered a national security threat, which made the images unclassified. He stated that the information was provided online to assist contractors going into Iraq. He stated that there was more information available in the last few months than in the past fifteen years.

Dr. Haley asked whether there was archival data for March 10, 1991. Mr. Love stated that DOD's Deployment Health office knew where this information was stored, but most of it was still classified, although some of it was part of the 1994 Riegle report. He stated that it was subject to release because of the threat level decrease. He stated that he had been submitting Freedom of Information Act requests for five years and had been informed it was classified. Dr. Haley stated it would also be useful to look at the third week of January 1991. Mr. Love stated that he was studying the entire period of time troops were deployed. He stated the problem was getting hold of the data, especially meteorological data from higher elevations.

Chairman Binns said that he found the CIA satellite image of the oil fire plumes on March 11th particularly compelling evidence of the direction the wind was blowing at the time of the Khamisiyah demolition, and thanked Mr. Love for bringing this important information to the Committee's attention.

The meeting adjourned for the day at 5:25 p.m.

The meeting reconvened Wednesday, September 21, 2005, at 8:34 a.m.

Report of the Office of Research and Development

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

Chairman Binns introduced Dr. Kupersmith.

Dr. Kupersmith provided a general overview of VA ORD's program. (See Appendix A – Presentation 17.)

Referencing a comment by Dr. Kupersmith, Mr. Graves stated that the Committee has earned a justifiable reputation for being hypersensitive about PTSD in relation to Gulf War illnesses. He stated, however, that the Committee does not doubt that it exists, but has concerns when PTSD is used as diagnosis for everything. Dr. Kupersmith stated that he understood.

Dr. Melling asked Dr. Kupersmith to clarify how much direction VA ORD was able to give to its researchers with regards to future research focuses. Dr. Kupersmith stated that it was limited. He stated that they could guide the researchers, but that they couldn't force them to do research that they didn't want to do. He stated that VA researchers all have academic appointments in universities. He stated one of the key elements in recruiting the highest quality physicians to VA has been the research program. He stated this is one of the purposes of the research program and that some may believe it is the most important. He indicated that if they started to force individuals to do research they didn't want to do, they would leave the VA. He commented that, as a dean of a medical school, he learned about "herding cats." He stated that clinicians' salaries did not depend on their research but that basic scientists' salaries did depend, in part, on the research program. He stated that a little more guidance could be provided for them.

Ms. Knox stated that she had worked in the VA as both a nurse and a nurse practitioner. She agreed that VA had contributed to medical discovery and knowledge. She encouraged Dr. Kupersmith to think about ways to make the VA more attractive to physicians so they are rewarded for their service. She referenced Dr. Kupersmith's comments about linking clinical records to research efforts. She stated that many Gulf War veterans had left the system because of access problems and are in need of treatment. She stated it was frustrating to meet veterans who were simply looking for help. Dr. Kupersmith stated that they could only deal with the records they had. He stated that 7 million veterans were being seen by the VA, and this was enough to do many types of studies.

Dr. Kupersmith stated that he believed that things had improved with VA physicians' response to ill Gulf War veterans. He agreed that if an individual went to any physician, not just VA physicians, with symptoms that the physician didn't understand or believe, the patient wouldn't get proper care. He commented that physicians needed to learn how to deal with this as a profession. He did note that VA hoped to bring more specialists into the system through increased Congressional funding. He stated that, based on his observations, the VA system had been revolutionized by the electronic records database. He stated that things were changing in the VA, and outside caregivers were looking to the VA for guidance.

Chairman Binns referenced Dr. Kupersmith's presentation comments about how VA research could benefit from the clinical experience. Chairman Binns noted that VA's current clinical guidelines for Gulf War illnesses were still based on theories of stress. He stated that physicians in the field still have the opinion that these were just difficult patients. He stated that the guidelines needed to be reviewed in order

to get better research feedback and more veterans coming back to VA for treatment. Dr. Kupersmith agreed, and stated that guidelines were meant to be revised.

Dr. Meggs noted that some physicians go out and find answers when he or she has a patient with symptoms that can't be explained. He stated that there has been an institutional attitude against these patients and understanding their conditions. He told a story about a discussion with an elder statesman in medicine who studied lupus back when it was a disease that wasn't understood. This physician was told early in his career not to do research in this area, when lupus patients were treated much like Gulf War patients are today. Dr. Meggs stated his belief that Gulf War illness could be figured out, but it would take the right attitude to move in the right direction.

Dr. Kupersmith stated that he was just talking "on the average." He related his experiences dealing with cardiology patients whose conditions were due to metabolic disorders. He stated that these syndromes were very hard to detect, but the patient's pain was real and should be treated as a pain syndrome, even if the disease wasn't fully understood. He acknowledged that there were many patients who "bounced" from physician to physician looking for help and relief.

Ms. Knox agreed with this statement, and asked for Dr. Kupersmith's help to facilitate the care of Gulf War veterans. She referred to Dr. O'Leary's tissue bank presentation. She noted that fifteen years had passed, but there was still no protocol for these veterans to donate their organs. She stated that Dr. O'Leary had referenced being in his job for 18 months and would have to ask what methods were currently available. She stated her hope that Dr. Kupersmith had colleagues to bring into VA ORD who could help get things moving. She stated that in the private sector, it would not be acceptable if an individual could not answer questions about their program after 18 months. Dr. Kupersmith jokingly said that universities didn't work that quickly either, but acknowledged that Ms. Knox had made a good point about tissue banks.

Chairman Binns stated it was depressing that he had to reiterate what he had said at the Committee's first meeting. He had hoped to engender a sense of urgency for research on Gulf War illnesses. He stated that, to some degree, the Committee had slipped into accepting the pace of change that is historic in this area, which was almost none. Veterans want to see someone taking a proactive stance, seeking to solve this problem in a logical way. Chairman Binns encouraged Dr. Kupersmith to put his staff to the position that they needed to solve this problem. Dr. Kupersmith stated that VA ORD couldn't force researchers to do research they didn't want to do. He stated that he needed to figure out ways to encourage them to get involved in this research, but couldn't promise that the research would be done quickly. He noted that the VA was a single entity, and there were many other entities that fund research. He suggested working to get the National Institutes of Health (NIH) interested in this area. He also suggested seeking industry support because it has the largest pool of research funds. While Gulf War veterans aren't a large enough population to garner industry's interest, their diseases (chronic fatigue syndrome, fibromyalgia, irritable bowel syndrome, etc.) do affect a much larger population.

Mr. Robinson stated that he appreciated Dr. Kupersmith's academic view on this issue but that it didn't translate into what veterans needed. He noted that Secretary Principi had stood up publicly and announced that Gulf War veterans' illnesses were a real problem. Further, Secretary Principi said research was needed and would be done with designated funds. However, this research has not happened. Mr. Robinson stated that veterans had heard the platitudes of many administrators over the last 5-7 years that he had been involved in this issue. He stated it was time to stop hearing what couldn't be done. Instead, they needed to hear what could be done.

Dr. Kupersmith stated his belief that he hadn't been saying "what couldn't be done." Acknowledging he might be sensitive or just plain tired of hearing "no", Mr. Robinson stated that he heard Dr. Kupersmith to say that VA researchers could not be forced to do this research. Mr. Robinson said that he disagreed, and noted that the Secretary had made the promise that the research would be done. Further, if the VA researchers weren't interested in doing this work and the 5/8th rule prevented the work from being done, then we needed to find a way to get it done, including going back to Congress if need be. He stated the way to encourage researchers to do this work was to educate them about the emerging science in this area. He stated that VA clinicians/researchers had no clue about the Committee or the science it is reviewing, nor was VA promoting this information to their clinicians. He said that this "engine" or area of research needed to be restarted after losing a lot of traction and momentum. He noted that this was due to several unfortunate events, some of which might be criminal in nature, i.e., violations of public law. He went on, though, to say that he was encouraged that Dr. Kupersmith was taking over the CRADO position. Dr. Kupersmith expressed his uncertainty at this comment. He stated that he didn't believe he had said this task couldn't be done. He said that if VA researchers were told that they had to do this research, and subsequently left, then veterans would be harmed. He believed that more could be done to educate VA physicians and encourage them to pursue research in this area. He stated that this was currently happening. He noted that the last research funding announcement (RFA) had solicited more and better proposals. He believed the next RFA would do even better. He stated that as a physician he didn't want to "do harm," and didn't want to harm the system. Mr. Robinson stated the military was similar, i.e., in wanting an all-volunteer force. He stated that he didn't want to force VA researchers to do research they didn't want to do. However, if VA clinicians weren't educated about the issues, they would never be interested in doing the research. Dr. Kupersmith agreed that education was important.

Dr. Meggs commented that he kept seeing smoke and mirrors used by administrators and researchers when it came to Gulf War illnesses. He stated that there were a large number of ill veterans, but the system and sometimes the research was designed to exclude them. He hoped that all concerned could get beyond this and quit dismissing these veterans. Dr. Kupersmith agreed that these difficulties were there, and that education was the first step. He noted that there were many conditions that weren't accepted early on by physicians, but later determined to be real. He related a story about the first description of a heart attack in 1911. He stated that most people fell asleep during the presentation with only one question raised during the discussion. He stated that the problem was analogous to other conditions, but that there were also a lot of political and military culture overtones for this issue.

Mr. Steve Smithson asked Dr. Kupersmith how he intended to have ORD encourage and educate clinicians. Dr. Kupersmith stated that they had a number of vehicles, including on-line and telephone options. He stated that none of these had been used to their full potential in this area. Chairman Binns commented that one of the VA officials involved in this process had referred to the Committee's report as "a waste of a lot of trees."

Dr. Haley commented that the last slide in Dr. Kupersmith's presentation was very encouraging. He understood that Dr. Kupersmith believed the objective was to inspire VA scientists to look at this as a disease, analogous to PTSD, and inspire them to find biomarkers and treatments for this disease, which may be one of the biggest new problems facing veterans in our lifetime. He stated that Dr. Kupersmith was the first CRADO to say this. Dr. Haley believed this was a new vision for VA ORD, and if this message could be carried forward to the field along with the Secretary's commitment of research funds, many VA researchers would jump forward to work on this problem. Dr. Kupersmith noted that this was an issue that would interest investigators. Dr. Haley agreed, and commented that it was intellectually challenging.

Ms. Knox stated that it wouldn't be a new day if the VA clinicians/researchers think Gulf War illness was just fibromyalgia, chronic fatigue syndrome, PTSD, etc. She stated it would be a new day if they think it is a brain disease. Dr. Kupersmith agreed, and stated that the point of seeking biomarkers was to provide a scientific basis for research. Dr. Haley stated that the education task may be very simple if ORD sincerely articulates this idea and the funding options to its researchers.

Dr. Melling commented that he personally understood how difficult it could be to change institutional researchers' directions or focus. He agreed that education and motivation was the key. Another key thing was to get the message across that this issue was not going to go away, nor would the direction change when administrations changed. Dr. Kupersmith found this to be an interesting point. He stated that the stability of VA ORD was very important in this matter too.

Chairman Binns reiterated Dr. Haley's point that this is one of the major health problems of veterans of our generation. He stated that the size of the problem is one of the major disconnects between what research shows and what most people within VA believe. He noted that, during an earlier private meeting, Dr. Kupersmith had been impressed by the high incidence of chronic fatigue syndrome (1.6%, which was 40 times greater than normal) among Gulf War veterans. He stated that these were the numbers that VA staff focused on, rather than the epidemiological research showing that 25%-32% of veterans are affected. He stated that Dr. Kang would be giving a presentation later that morning regarding the initial results of his most recent Gulf War veteran study. He stated that Dr. Kang had found: (1) 35% of Gulf veterans have multisymptom illnesses as defined by the study and (2) 10% of the controls met this definition. Thus an excess of 25% of veterans who served in the Gulf War were affected by these conditions. He stated that VA now had its own research that supports a 25% causality rate within that war, which evidenced a huge problem. If VA ORD would simply trumpet this research when it is published, it would change a lot of people's attitudes. Dr. Kupersmith stated that this was a good point, and that VA staff wanted to work on things that were important to treating veterans.

Chairman Binns thanked Dr. Kupersmith.

Gulf War Update

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

Dr. Goldberg gave an update on the progress of VA ORD's research program for Gulf War illnesses, including funding levels and announcements for FY2005. (See Appendix A – Presentation 18.)

Mr. Graves asked if the Committee would be able to review the projects included in the Gulf War research portfolio. Dr. Goldberg stated that he would be happy to supply the Committee with a list of the current, on-going Gulf War research projects. Dr. Steele stated that this information had been provided to the RAC office and had been distributed to Committee members at the meeting [See Appendix C.], but that the funding numbers were slightly different from Dr. Goldberg's presentation slides. Dr. Goldberg acknowledged that the funding numbers in his presentation were slightly lower. He explained that 9.3 million dollars had been spent on these projects in FY2005. FY2006 costs would be higher, because some projects started late in FY2005. FY2006 would be the first full year of funding for these projects. Dr. Goldberg noted that it was better to fund projects at the start of the fiscal year because it ensured that projects get started early and work gets done that year. Dr. Goldberg stated that FY2005 RFA-funded projects would start on or after October 1, 2005. He said the number of projects and total monies granted under this RFA depended on the quality and relevance of the proposed studies. He stated that some

proposed projects might be considered tremendous science, but completely irrelevant to Gulf War illnesses, and so would not be funded under this RFA.

Dr. Goldberg stated that two Gulf War initiatives were currently on the table: the Gulf War Treatment Research Center and the reissuance of the Gulf War Merit Review RFA. He stated that ORD had made a commitment to reissue the Gulf War Merit Review RFA for FY2006. He asked the Committee to provide ORD with suggestions on how to fine-tune the RFA announcement, including issues that needed to be specifically addressed. He suggested including a provision for studies similar to Dr. Proctor's GIS research.

Mr. Robinson thanked Dr. Goldberg for the overview of ORD's research funding process and the relevance priority given to planned or proposed research initiatives. He stated that he looked forward to the Committee being more informed and involved in the Gulf War RFA fine-tuning process. He asked Dr. Goldberg for his understanding of the Committee's mandated role as it pertains to proposed research and research directives for Gulf War veterans. Dr. Goldberg stated that he understood the Committee to be a Federal Advisory Committee, tasked with giving advice, and that ORD was to listen to this advice. He stated that the Committee was to look at the current research, speak with scientists, have discussions in a public forum and formulate recommendations which go to the Secretary and the CRADO to help direct policy. Mr. Robinson stated he was asking these questions so veterans in the audience would understand the Committee's relationship with ORD.

Mr. Robinson noted that the Committee had submitted a list of suggested scientists to be considered for the Gulf War Merit Review panels. He asked where this process stood and whether any of these individuals would be serving on the panels. Dr. Goldberg acknowledged that the first panel hadn't included any, but noted that the second panel included four members from the list. He stated that the list had been used in the recruitment process, but many individuals weren't able to participate for a variety of reasons, e.g. not available for a particular date, involved in teaching or current NIH committees, etc. He stated that researchers were matched to proposals within their area of expertise. He stated that the suggested list didn't contain many whose research expertise was on point with the proposals to be reviewed by the first panel. He stated that the second panel would address neurological, cognitive, and neurotoxicology proposals, and thus would include some individuals suggested by the Committee.

Dr. Steele stated that the Committee had previously heard concerns from field investigators about submitting Gulf War illnesses research proposals for review, only to have them reviewed by individuals who had no experience in Gulf War-related illnesses. She stated that, based on her review of the first study section roster, she wasn't familiar with any of the panelists' names being involved in Gulf War research. Dr. Goldberg disagreed and stated that a number of these individuals had been involved in this area of research. He stated that some were clinicians who could provide guidance on proposed treatment studies and that a variety of individuals were appointed to this panel in order to identify good projects. Dr. Steele noted that the whole purpose of having a special Gulf War research study section was to include researchers with familiarity and experience in Gulf War research. She understood the need for broad expertise on these panels, because of the diverse nature of the proposals. However, to meet the intended purpose of the review panel, some of the researchers needed specific expertise in Gulf War illness research. Dr. Goldberg stated that the panel's charter required the panel to review the quality of the science behind the proposals and that the panels were organized to do just this. Chairman Binns noted that the only reason that these new Merit Review panels were created was to give these proposals special attention. Dr. Goldberg agreed, and stated that it pulled the proposals out of the general project mix and gave them a clear and special hearing. He also indicated that scientists on the panel had outstanding credentials and the requisite expertise

Department of Veterans Affairs Secretary Jim Nicholson arrived at the meeting and was welcomed to the proceedings by Chairman Binns.

Secretary Nicholson thanked Chairman Binns for his leadership of the Committee and his dedication and commitment to this cause. He apologized for not being able to meet with the Committee at its April 2005 meeting. He explained that he had been called away due to Pope John Paul II's funeral. He commended the Committee for its work and commitment to exploring every avenue of science in pursuit of answers to questions that continue to evade us. He stated that the first Gulf War may no longer dominate our news, but there was a common thread between it and the current war. He noted that many of today's servicemen and women were probably being exposed to many of the same conditions and health hazards.

Secretary Nicholson stated that it was common sense that there were veterans who were ill as a result of their service in the Gulf War, and these veterans and their families should have no doubts as to whether their government was committed to getting to the bottom of this problem. He noted that VA currently compensated 4,000 Gulf War veterans for undiagnosed illnesses, but acknowledged that number was overshadowed by the legions of veterans who believed that their health was also compromised as a result of their deployment. He acknowledged that they may also believe that the VA is not doing enough to answer their questions. He noted the misshapen body of misinformation, legends, myths and distrust would grow larger as it took longer to provide definitive answers to these questions. He stated that the symptoms and illnesses needed to be accounted for, and there was a great need to understand the long-term health implications associated with veterans' contact with a diverse catalog of naturally-occurring and human-introduced physical and mental threats.

Secretary Nicholson questioned how we could be sure that we were protecting the health of today's Armed Forces if we didn't understand the threats to yesterday's war fighter. He wondered how we could expect today's citizen soldiers to have faith in their government's ability to meet their post-deployment health needs if the government hadn't provided enough evidence that it could take care of yesterday's veterans.

For these reasons, he stressed that the Committee's work was very important. He stated that it was of great concern for those affected, but it also held strategic importance to our country and its defense. He noted that the Committee's frank assessments and communication with him, as well as his team, were extremely important. He stated that there was a need for new, good, on-point research ideas that used the appropriated funds in the best way possible and in line with the goals established. He stressed again how important the Committee's work was in accomplishing this goal, and thanked the Committee for its service.

Chairman Binns asked if Secretary Nicholson had time for a few questions from the Committee. Secretary Nicholson stated he had another engagement, but agreed to take a couple questions. Before doing this, Committee members introduced themselves to the Secretary.

Mr. Robinson personally thanked Secretary Nicholson for taking an interest in this issue, and expressed his regret, but understanding, that they hadn't been able to meet earlier to discuss certain issues. He expressed concern that progress in this area had slid backwards during the administration transition between Secretary Principi and Secretary Nicholson. He stated his concern, which he believed Secretary Nicholson was aware of, that promises made by Secretary Principi for research and funding had not yet been achieved.

Mr. Robinson stated that the Committee, by its authorizing legislation and charter, was supposed to have complete access and be a full partner in anything and everything the VA did in relation to Gulf War

research. He stated that this was not happening. He expressed hope that, under the new leadership of the CRADO and the Gulf War portfolio manager, it would be a new day. However, he noted that some things had happened within the VA, which Secretary Nicholson might not be aware of, that may in fact be violation of public law. He stated that the Committee had been circumvented by individuals within the VA who formed an IOM panel during the transition between administrations, and seemed to take Gulf War issues light years backwards. He thought that these actions might be a violation of the Committee's charter and authorizing public law. He stated his wish to speak with the Secretary about this in more depth at a later time. As a final point, he stated that one of the biggest problems in enticing good scientists and encouraging good research in this area was the VA's failure to promote the Committee's work. He stated that VA staff needed to be educated about the Committee's recommendations. One of the avenues for this type of education was the Veterans' Health Initiative (VHI) series on Gulf War veterans' illnesses, which Mr. Robinson stated was very outdated and contained very old ideas. He concluded by thanking Secretary Nicholson for his leadership and attendance at the Committee's meeting, and expressed his hope that the Committee could fulfill its intended purpose, i.e., provide advice and guidance as a full partner in planning the direction of research for Gulf War veterans.

Ms. Knox thanked Secretary Nicholson for meeting with the Committee. She stated that Secretary Principi's support of Gulf War veterans had been exciting and stimulating. She indicated that she didn't want her comments to be viewed as a complaint, but rather wanted to stress the importance and urgency of Gulf War veterans' concerns. She noted several veterans wished to donate their organs for research, but action to get this program started and protocols established had been difficult. She hoped that some of these broad research ideas would be made available at the patient level. She noted that there would be no one to function in the next war if current veterans did not receive the care they deserve. There would no longer be a voluntary military service. She noted that veterans were seeking health care outside of the VA to get answers to their questions. She hoped that the Committee would have input that is actually implemented in the funding of these new research ideas. She expressed her belief that if VA employees knew that Secretary Nicholson believed that Gulf War veterans' illnesses were a neurological disease, they would be excited about this and not look at the condition as just fibromyalgia or some unknown chemical multisymptom disease. She stressed that veterans wanted answers.

Chairman Binns assured the Secretary that the Committee was not unappreciative of the good work being done at VA. He noted that several distinguished VA researchers had spoken over the course of the past two days. He stated that their findings were important and hopefully would convince any doubters, along with Secretary Nicholson's leadership, that this is an issue worthy of study. He noted that Dr. Han Kang would speak later that morning and that he would present evidence that 25% of deployed Gulf War veterans are ill from chronic multisymptom conditions due to their service in the war. He stressed this was a huge casualty rate, and was a cause worthy of the VA's attention. Secretary Nicholson agreed.

The Committee thanked Secretary Nicholson for his time. Secretary Nicholson left the meeting.

Dr. Goldberg returned to the podium for questions.

Dr. Melling noted that one of Dr. Goldberg's goals was to stimulate more proposals. He indicated that he wasn't sure how VA's phone system worked, but noted that the Government Accountability Office (GAO) sent automatic voice messages from the Director General, addressing all researchers on a particular issue. He found hearing the Director General himself talk about an opportunity or issue sent a very powerful message. If this could be done within VA, he encouraged Dr. Goldberg to do this. Dr. Goldberg stated that the bad news was "if you have seen one VA, you have seen one VA." He went on to explain that the VA's phone system didn't allow him to pick up a phone and send a voice mail to every VA phone. He noted that he had the means to directly communicate with every VA research program.

He stated that this mechanism hadn't been employed sufficiently or as often as it should have been. However, this would change in the future. He acknowledged that ORD was the heart of the VA research program, and was the point of contact between the researchers and Central Office. He noted though that local VA research offices could send messages from their offices to all researchers at their medical centers. This would allow messages to be disseminated in a two-step chain.

Ms. Knox expressed confusion as to why funded projects were being held up because applications were not finished or lacked signatures. She thought once the deadline had passed, "the door had closed." Dr. Goldberg stated that that was true, but there were provisions that allowed a grantee to finalize administrative technicalities and hurdles after the deadline. The grantee just wouldn't get the monies until this compliance work had been finished. He indicated that NIH had a similar provision.

Dr. Haley agreed that bringing a grant application into compliance was a time-consuming process, and related a personal situation where it took 11 months to get DoD grant monies. This was because three institutional review boards (IRBs), including DoD's own IRB, had to review the project. Dr. Haley stated this type of delay was a problem, but it was a known problem. He stated that the real problem was acknowledging that Gulf War illnesses research was a legitimate area of study. He indicated that there was contempt towards this type of study. Leadership in ORD needed to create a vision among its researchers that this is an intellectually stimulating area of research and this would be where the "game was won." As for compliance issues and delays, Dr. Haley indicated these were not a real problem.

Dr. Haley stated that the other major problem, or stop-gap, in this area of research had been the peer-review grant committees. Before the Gulf War Merit Review Panel, Gulf War illnesses proposals were being reviewed by general medical committees, e.g., gastroenterology, etc. If the members of these peer-review committees knew nothing about Gulf War illnesses, they were not likely to fund studies in this area.

Chairman Binns noted that the meeting was running late, and that Dr. Kupersmith had another meeting to attend. Chairman Binns and the Committee thanked Dr. Kupersmith for speaking with the Committee that morning.

Dr. Goldberg expressed his understanding as to the frustration and disruption that accompanies constant high-level administration turnover. Dr. Steele noted that it was disruptive to progress as well.

Commenting on an earlier point made by Dr. Goldberg, Dr. Steele agreed that RFAs needed to be more focused, with specific questions of interest being posed. She noted that, in earlier RFAs, the Committee had advised that this needed to be done. She stated that she was glad to hear that this is what Dr. Goldberg wanted to do with future RFAs. She was even more pleased to hear that Dr. Goldberg would speak with specific researchers to encourage them to investigate specific issues related to their expertise. Dr. Goldberg indicated that he could notify researchers of these opportunities.

Dr. Goldberg commented that NIH funding rates were decreasing, and many researchers were not pursuing these grants due to the low odds of being funded. He stated the funding rate for Gulf War proposals were historically higher than other areas of research at VA. The funding rate for the FY2004 RFA was 28.6% but that other review panels were funding at a rate of 22%, and as such Gulf War illnesses would become attractive to researchers. Dr. Steele appreciated that the proportion of funded Gulf War illnesses studies had started to go up in FY2004.

Dr. Steele noted Dr. Goldberg's commitment to review the research portfolio to determine if all included projects were really relevant to Gulf War illnesses. She stated that the Committee had reviewed the

funding for FY2005, and that many of the projects identified did not appear to be specific to Gulf War illnesses. (See Appendix C.) She asked Dr. Goldberg if he had thought about the process he would use to determine whether these projects were relevant or not. Dr. Goldberg stated that he would start by pulling the abstracts for every project. Dr. Steele asked if he had thought about the criteria that would be used to make determinations of relevance. Dr. Haley indicated that the Committee could advise Dr. Goldberg about the questions that needed to be answered, along with how to detect non-relevant research disguised as Gulf War illnesses research. Mr. Robinson stated that this was his understanding of what the Committee was supposed to be doing. In other words, the Committee would have some knowledge of the proposals and be able to give an opinion, not make decisions, about research proposals.

Chairman Binns stated that the sad aspect of the FY2004 RFA funding story was that, while there were a higher number of projects funded, over half were related to stress-based theories. He stated that was why the FY2005 RFA specifically excluded these types of studies. He noted that the Committee had heard presentations on some of the funded proposals at the East Orange, NJ, War-Related Illness and Injury Center, and had found some of them "fanciful" at the time. He stated that 28% was a good funding rate, but it didn't necessarily satisfy the quality or relevance elements.

Chairman Binns appreciated and sympathized with Drs. Kupersmith's and Goldberg's position of taking over a situation where there has been lots of turnover and lack of staff. However, there had been an Acting CRADO and other officials who held these offices since Secretary Principi and Chairman Binns stood in that room before the press and public and committed to spending up to 15 million dollars in new FY2005 research. He noted that FY2005 was basically over, and projects funded under the FY2005 Gulf War illness RFA had not been awarded yet, nor had the treatment research center RFA been announced. He did not fault Drs. Kupersmith or Goldberg, but predecessors in their positions had been aware of the commitments made and these commitments have been totally unmet. He stated his concern that this "lost" year was being allowed to be lost, and that there would be no effort to make up for lost time. He stated that proposals submitted under the FY2005 RFA wouldn't be funded until 2006, and the FY2006 proposals wouldn't be funded until 2007. Dr. Goldberg stated that this was a typical time schedule for processing an RFA. Chairman Binns again stressed that a year had passed, and nothing was in place to meet or catch up to research funding commitments that had been made.

Dr. Steele noted that there needed to be assurances that this slow action would not continue. Dr. Haley stated this raised the question as to whether the FY2006 procurements could be more expeditiously done so they were awarded in FY2006. Dr. Goldberg stated that the plan was to get the treatment research center RFA out as quickly as possible, with the intention of getting those started in FY2006. This was his first priority, followed by the FY2006 RFA. He stated that they would not be artificially delaying the submission date for the FY2006 RFA or the timing of the review to force funding in FY2007.

Dr. Haley suggested that, if the ORD office was understaffed, the Committee might need to make a recommendation to the Secretary that additional staff be hired to get this job done. He stressed this was the greatest health threat to veterans to have occurred in recent times, and that it needed to be addressed. If additional staff was needed to handle the workload, the Committee needed to advise that more staff be hired.

Ms. Knox stated that the Committee needed to help devise solutions to getting more research proposals. Dr. Goldberg stated that better communications should dramatically increase the number of submissions. Ms. Knox asked Dr. Goldberg about the communication methods he would be using. Dr. Haley stressed that it wasn't just communicating that there is an RFA, but also the vision of what needed to be done. Dr. Goldberg stated that the first step was to communicate with the research offices of the 70-odd medical

centers with active research programs. He hoped that the RFA would also give much better guidance on the type of research needed.

Mr. Robinson stressed that Dr. Goldberg should become involved in the VHI series, because this is the document to which VA clinicians and researchers refer for treatment options and information on the status of Gulf War veterans' illnesses. He noted that the current guidelines are 10 years out-of-date.

Dr. Melling suggested that a letter go out from Secretary Nicholson to the VA research community, in which the Secretary stressed the importance of this research. Mr. Smithson noted that Secretary Principi had made a video in a previous year, attempting to change this attitude and encourage researchers to apply for these grants. He asked if ORD had sent this out to the VA research community. Dr. Goldberg stated that he couldn't' answer this, but felt it was probably in the same category as the RFA. If someone wants to look at it, it is there. He stated it hadn't shown up as an e-mail attachment to every VA researcher. He stated that the system, up to this date, had been quite passive, and that it was his responsibility, as the new portfolio manager, to make the communications more active. Ms. Knox stated she liked this attitude. Dr. Haley commented that he thought this video had made some rounds among researchers. With better RFAs and Dr. Kupersmith talking about biomarkers, etc., he felt this would do the most to encourage good proposals.

Chairman Binns noted that this was the same problem faced by the Committee. The Secretary of the Department of Veterans Affairs had put together a video showing that he was completely behind Gulf War illnesses research, and it was sent out to the field. So, the VA research community had heard this message before. He noted that, at the same time, when a VA researcher called ORD and asked if special attention was going to be paid to Gulf War illness proposals under the Deployment Health RFA, he would be told by the then portfolio manager that no special consideration would be given these proposals. He stated that, if the Committee was going to tell veterans that progress was being made, there needed to be action to back up these statements. He went on to say that, even if there was a new video made by Secretary Nicholson, its effect had already been diluted because of the failure in the past enforcement of this message. He stressed that, at this point, the only thing people would believe would be action. Dr. Goldberg stated that he couldn't argue with this.

Dr. Goldberg stated that he had looked at the FY2005 funded project list, along with the proposed FY2005 projects. He believed that the quality, relevance and types of projects submitted in FY2005 were much better. He thought researchers understood how important this research was by ORD simply issuing the RFA a second time. He believed researchers would realize that ORD was really serious about this research when the RFA was released the third time. He didn't want to say that researchers were mercenaries, but they would follow the money in the long run. He noted that researchers' focuses change or evolve over time, and they will apply their knowledge and techniques to new areas in order to maintain their sanity and the health of their laboratory. He cautioned that this change wouldn't happen overnight, but it would happen. It was his job to make sure that path was there, visible and unimpeded. He commented that "if you build it, they will come." Mr. Smithson noted that Dr. Goldberg also had to let them know that it was being "built."

Chairman Binns invited public questions.

Ms. Nichols suggested the following to Dr. Goldberg: (1) VA sponsor a conference on Gulf War Illnesses. She stated it had been almost four and half years since the last conference, and it might trigger some new research; (2) VA research publications should announce these RFAs and review what had been learned; and (3) the Committee should be utilized to get this information out to the researchers. She

suggested having Drs. Steele or Golomb do a segment for the VA's television network on these matters, in an effort to start a dialogue between researchers, the Committee and ORD.

Ms. Hammack suggested that VA's Public Affairs office be utilized to get this message disseminated. She noted that printed media, not just electronic media, needed to be utilized. She listed two printed periodicals, VA Guardian and US Health, as being possible target publications.

Ms. Hammack asked Dr. Goldberg if he interacted with Dr. Mark Brown and the Deployment Health Working Group. Dr. Goldberg stated that, as the Gulf War Illnesses Research Portfolio Manger, he had a position on the research subcommittee and was responsible for putting together its next report to the Congress.

Chairman Binns asked what responsibilities the Deployment Health Working Group had that didn't include Dr. Goldberg. Dr. Goldberg stated that many of the discussions dealt with seamless transition and were focused on issues affecting the current deployment. Dr. Steele asked if there was only one VA representative on the main committee. Dr. Goldberg stated that there were a number of VA representatives, including Drs. Mark Brown, Craig Hyams, and Susan Mather. There were also DoD representatives and a liaison from MoD.

Chairman Binns thanked Dr. Goldberg.

The meeting adjourned for a break at 11:05 a.m.

The meeting reconvened at 11:23 a.m.

Preliminary Findings: Reported Unexplained Multisymptom Illness Among Veterans Who Participated in the VA Longitudinal Health Study of Gulf War Era Veterans

Dr. Han Kang, DrPH
Director, Washington, DC, War-Related Illness and Injury Study Center
Environmental Epidemiology Service, Department of Veterans Affairs

Chairman Binns introduced Dr. Kang. He noted that Dr. Kang was the first researcher within VA to step forth and take the kind of proactive effort that the Committee had been encouraging this morning. Dr. Kang had a study that was well underway, with the questionnaire already sent for OMB approval and printing. He volunteered to bring it back, found ways to finance the additional costs, and included several pages of questions recommended by the Committee. The Committee commended and thanked Dr. Kang for his work.

Dr. Kang gave an overview of his group's preliminary findings with respect to unexplained multisymptom illness among Gulf War veterans and the effects of various practices and treatments on their symptoms. (See Appendix A – Presentation 19.) He explained that the data analysis in this study was complex because the questionnaire responses relating to treatments were open-ended and handwritten, not the pre-structured, machine-readable responses that are typically used.

Mr. Graves asked if any of the era veterans received vaccinations, but weren't deployed. Dr. Kang stated that this was addressed earlier in the study. Discussion occurred as to whether there were vaccinated veterans who didn't deploy. Mr. Smithson commented that DoD's position was that there was a very small percentage of non-deployed, vaccinated veterans, because most were vaccinated in theater. Mr. Graves stated that his unit received their vaccinations before deployment, and there were individuals who

didn't deploy. He noted this was significant and these veterans needed to be identified because it might explain why some of the era veterans has multisymptom illnesses.

Mr. Graves also asked if the questionnaire included questions about whether cost affected veterans' choice of treatment or therapy. Dr. Kang stated this question was not asked. Mr. Graves noted that the high over-the-counter drug usage might be explained by their lower cost compared to the other listed therapies.

Dr. Melling asked whether there was any indication that era veterans had symptoms that began before 1991, and then rolled over into the first part of the study. He stated this might explain the higher numbers immediately following the war. Dr. Kang stated that they had this information from an earlier part of the survey, and could pull this information out for review. Dr. Haley stated this was a very good point, and may indicate that there is a different profile in the deployed and non-deployed with respect to pre-existing symptoms.

Dr. Haley commended Dr. Kang on this study. He stated that this was a tremendous survey, and noted that this was one of the first Committee objectives to be recognized by a VA researcher. With respect to future, more in-depth analyses, he suggested pulling out the information on the people who got "well" and "better" versus those who believed they hadn't gotten better. He stated this might help identify treatments that provide veterans with long-term benefits, and help the Committee guide the VA with respect to clinical research trials. He stated this might be the "ultimate fishing expedition" with the hope of finding a useful treatment. Dr. Steele reiterated that this study was a great contribution to Gulf War illnesses research. She noted the contribution was even more than the Committee might realize, because of the difficulty of analyzing open-ended questions on the large sample.

Mr. Robinson commented that these findings were relevant to previous studies regarding cognitive behavioral therapy. He asked Dr. Kang if this survey asked veterans whether they were VA patients or had sought treatment outside the VA. He noted that some of the treatments listed from the survey are not provided by VA. Dr. Kang stated that this information could be acquired because the survey participants could be matched with the VA's treatment database.

With respect to Gulf War veterans finding benefit from drug therapy, Mr. Robinson noted it was interesting to see "illegal drugs" listed as a treatment. He stated that the use of opiates could mask pain, which may be beneficial, but it didn't cure the underlying condition. He stated that he knew several Gulf War veterans who used marijuana, alcohol, etc., because they couldn't get opiates in the VA healthcare system. Their use of these drugs may provide them with a way to survive another day.

Mr. Wesley commented that opiates hadn't helped his condition or pain. He stated it simply provided him with a drug-induced "high", which prompted him to discontinue taking it.

Ms. Knox suggested that the Committee ask the Secretary about mechanisms available to reward researchers, such as Dr. Kang, who have made ground-breaking contributions to Gulf War veterans' research. Chairman Binns indicated that there might be a way the Committee could establish a certificate of appreciation.

The meeting adjourned for a break at 12:07 p.m.

The meeting reconvened at 12:20 p.m.

RAC Committee Business

Lea Steele, PhD
Scientific Director, RAC-GWVI

Dr. Steele outlined proposed plans for upcoming Committee meetings and reports. (See Appendix A – Presentation 20.)

Dr. Haley suggested the Committee address the occurrence of psychological symptoms and states that accompany brain disease. He noted that a high percentage of really ill Gulf War veterans have depression. He noted that a couple of studies show that there is a slight excess prevalence of mania in Gulf War veterans. He believes this had fueled the premise that Gulf War illness is a psychological disease. He noted, however, that 80% of individuals with Multiple Sclerosis (MS) develop depression, compared with 5-10% of individuals who don't have a neurological disease. He commented that no one believes depression causes MS. Psychological symptoms are more likely to appear when certain parts of the brain are affected. Dr. Steele agreed and stated that the point was made in the Committee's 2004 report. She noted this connection was especially pronounced in individuals with toxin-induced encephalopathies.

Ms. Knox commented that a new drug, Cymbalta, treated both depression and diabetic peripheral neuropathic pain. She noted that if there wasn't enough norepinephrine or serotonin within the prefrontal cortex, the individual lacked the neurotransmitters that go to the basal ganglia. This was why the drug could be used for dual purposes. She stressed this drug treated a brain disease, with neurotransmitters lacking in the brain causing depression, and in the periphery causing pain. She stated that the two conditions could not be separated. Dr. Steele agreed and stated that the bottom line was that having psychological symptoms did not imply psychiatric etiology.

Dr. Melling commented that the Committee had looked at a wide range of possible causes for Gulf War illnesses. He commented that this field of research had been "bedeviled" because the illness was multisymptom with a multi-exposure trigger. He suggested that the Committee was in a unique position to weigh the various factors. Dr. Steele agreed and commented that previous review groups hadn't tried to weigh the strengths and weaknesses of the evidence for various exposures contributing to these conditions.

Chairman Binns stated that he was sympathetic to this approach. He noted that one of the comments/criticisms of the Committee's 2004 report was that it was unwielding with the number of recommendations made. He indicated that the Committee needed to focus on those areas that were most promising, and resist the temptation to improve every area.

Dr. Melling noted that the Committee was short two members. If the Committee did go through this exercise, he suggested that there be a couple new people at the table who could challenge the discussion by asking difficult questions. Chairman Binns agreed. He stated that recommendations for three new appointments had been submitted to the Secretary in Spring 2005. The process had not been completed for a variety of reason. He hoped that these appointments would be completed promptly and before January 2006, which is when the next round of appointments are due to expire. He stated that the Secretary was aware of the importance of this issue. He also agreed that the Committee could benefit from individuals with in-depth scientific expertise in the key areas, while maintaining the Committee's mix of veteran and layman input.

Mr. Graves asked Chairman Binns for his opinion as to why the new Committee appointments had been delayed. Chairman Binns stated that he had been hoping that there might be action before this meeting,

and had some individuals holding these dates in their schedules. He indicated that he did not know and thought it might not be useful to speculate on why it was taking longer. He agreed, though, that there needed to be a full Committee with people who have strong scientific backgrounds in the areas of interest and a view that Gulf War illness was a real problem, which needed to be solved quickly.

Mr. Robinson commented that veterans might not be aware of Chairman Binns' routine communication with the Secretary about the concerns of the Committee. He asked if the Committee should prepare an official document outlining these concerns for the Secretary. Mr. Graves stated that the Committee had sent such a letter to former Secretary Principi. Chairman Binns stated that he had no problem with doing this. He noted that the Secretary was aware of many of these concerns, but there was strength in a letter from the entire Committee. Ms. Knox commented that it was also important to note the VA's positive accomplishments in this area. Mr. Graves stated that a report to the Secretary would be a start to doing this. [Note: A letter from the committee was submitted to Secretary Nicholson on September 30, 2005. See Appendix D.]

Chairman Binns thanked Dr. Steele and the Committee staff for doing a fantastic job in coordinating the meeting. Mr. Robinson commented that the Committee's first certificate of appreciation should go to them. Chairman Binns noted that, in addition to work outlined in her last presentation, Dr. Steele was working in other capacities, e.g., working with Dr. Goldberg on the implementation of the treatment research center RFA, etc. He stated that he hoped, once VA was producing first-class Gulf War RFAs on its own, the Committee's time could be spent fully on looking at new research opportunities. Dr. Steele said Chairman Binns was kind to point out the work of the Committee staff. She commented that Committee members might not be aware of the time and extensive efforts devoted by Chairman Binns on behalf of the Committee's work. Chairman Binns stated that, hopefully, everyone soon could applaud the real mission of the Committee, i.e., making a difference in the health of Gulf War veterans. He appreciated Dr. Kang's presentation, and thought it was a good note on which to end the meeting.

Mr. Graves noted that veterans in the audience should also be commended for their time and commitment to this issue.

Public Comment – Day 3

Ms. Hammack spoke to the Committee. She asked if the Committee could investigate why Gulf War veterans were being told they couldn't donate blood today. She wanted to know why this policy was still in existence. Mr. Robinson stated that he was not aware of any current Red Cross, DoD, or VA regulation that prohibited these donations. He stated he would be willing to assist any veteran in finding out why they were being denied the opportunity to donate blood. He noted that when troops returned home in the early 1990s, they couldn't donate blood because of concerns about leishmaniasis and certain medications taken in theater. However, time has passed, and these concerns have diminished. Ms. Hammack stated that she had been to a U.S. Food and Drug Administration meeting in 2003, and they were proposing to continue the blood donation ban for Gulf War veterans because of leishmaniasis. Mr. Robinson stated that there is a two-year ban on blood donations for currently deployed military personnel, but not 1990-1991 Gulf War veterans.

Ms. Hammack stated that more information was needed about VA cooperative studies. She stated that the titles of these projects were known, but needed the Committee to recommend that VA clarify, implement, or create a policy that allows veterans to volunteer for these studies. Lastly, Ms. Hammack asked that the Committee make recommendations in its next report regarding the need for a VA Gulf War tissue bank.

Ms. Nichols spoke to the Committee. She thanked the Committee for listening to the veterans and allowing their input at meetings. She suggested that the Committee recommend merit review awards and promotions to reward outstanding VA researchers. She had hoped to learn about the proposals reviewed at the last Gulf War merit review panel at this meeting. Dr. Steele stated this information would be available after the studies were approved. Drs. Steele and Goldberg explained that the proposals were still being reviewed and wouldn't be approved until the second panel had met. Ms. Nichols asked for more specific information about the proposed treatment center. Dr. Steele explained that the RFA had not been finalized, but would be publicly available.

Ms. Nichols asked for a flow of information so the veterans could point out issues that might have been missed. She asked for more information about the Deployment Health Working Group meetings, e.g. when and where they are being held, if they were involved in the IOM contracting process, etc. She also inquired about the Committee's expert panel's activities. Chairman Binns stated that the Committee needed to make better use, in a formal way, of the expert panelists. He stated the panelists had been consulted individually on certain questions, but there had not been a formal process to solicit their collective wisdom. He noted that telephone meetings with each panelist had occurred very early after the Committee's inception (2002) to brainstorm ideas and get initial reactions. He indicated that a more regular and formal interaction was a good idea. Dr. Haley commented that Dr. Golomb, former RAC Scientific Director, had worked extensively with these panelists in 2002 to help form the questions addressed by the Committee. He stated that this was a very informative time, using the expertise of very prominent and knowledgeable neuroscientists. He noted that they hadn't been involved recently, but the Committee was still implementing the roadmap that was laid out back in 2002. Mr. Graves noted that their assistance was needed to focus the Committee's future work. Dr. Steele noted that the Committee did interact with these individuals informally, for advice on specific matters.

Chairman Binns thanked everyone for attending the meeting.

The meeting adjourned at 12:55 p.m.