Research Advisory Committee on Gulf War Veterans' Illnesses

April 6-8, 2005 Committee Meeting Minutes

U.S. Department of Veterans Affairs
811 Vermont Ave, Room 819
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 April 6-8, 2005, meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses.

_____

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

Table of Contents

Attendance Record

Members of the Committee
James H. Binns, Chairman
Beatrice Golomb
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
Daniel Clauw
David Barber
Iris Bell
Wayne Briner
John Grabenstein
Mark Melanson
Mary Ann Parkhurst
Phillip Pittman
William Reeves
Brian Schuster

Abbreviations

AChE	Acetylcholinesterase
ACR	Armored Cavalry Regiment
AFIP	U.S. Armed Forces Institute of Pathology
ALS	Amyotrophic Lateral Sclerosis
AVA	Anthrax Vaccine Adsorbed
CBT	Cognitive behavioral therapy
CCEP	Comprehensive Clinical Evaluation Program
CDC	U.S. Centers for Disease Control and Prevention
CFS	Chronic fatigue syndrome
CI	Chemical intolerance
COL	Colonel
CRADO	Chief Research and Development Officer (VA)
DESP	Deployment Environmental Surveillance Program
DoD	U.S. Department of Defense
DU	Depleted uranium
EBT	Exercise and behavioral therapy
FDA	U.S. Food and Drug Administration
FM	Fibromyalgia
fMRI	Functional Magnetic Resonance Imaging
GAO	U.S. Government Accountability Office
GWI	Gulf War illness
GWVIS	Gulf War Veteran Information System (VA)
HHS	U.S. Department of Health and Human Services
HPA	Hypothalamic-pituitary-adrenal
HSRD	Health Service Research and Development Service (VA)
IOM	Institute of Medicine
LOI	Letter of Intent
LTC	Lieutenant Colonel
MCS	Multiple chemical sensitivity
MMWR	*Morbidity and Mortality Weekly Report*
MP	Military police
NASA	National Aeronautics and Space Administration
NIH	National Institutes of Health
NOAA	National Oceanic and Atmospheric Administration
NGWRC	National Gulf War Resource Center
OEF	Operation Enduring Freedom
OIF	Operation Iraqi Freedom

ORD	Office of Research and Development (VA)
OSAGWI	Office of the Special Assistant for Gulf War Illnesses (DoD)
PA	Protective antigen
PTSD	Post traumatic stress disorder
RAC-GWVI	Research Advisory Committee on Gulf War Veterans' Illnesses
REAP	Research Enhancement Award Program (VA)
RFA	Request for Applications
RFP	Request for Proposals
UIC	Unit ID Code
UMRC	Uranium Medical Research Center
USACHPPM	U.S. Army Center for Health Promotion and Preventive Medicine
VA	U.S. Department of Veterans Affairs
VAERS	Vaccine Adverse Events Reporting System
VHI	Veterans' Health Initiative (VA instructional program for physicians)
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
Lafayette Building, 811 Vermont Ave. N.W. (Room 819) Washington, D.C.

Agenda
Wednesday, April 6, 2005

7:30 – 8:00	Informal gathering, coffee	
8:00 – 8:15	Meeting called to order Welcome, introductions, opening remarks	Mr. Jim Binns, Chairman
8:15 – 8:45	Overview: Multisymptom Illnesses in Gulf War veterans	Dr. Lea Steele, RAC-GWVI
8:45 – 9:45	Multiple Chemical Sensitivity: Research on Characteristics, Pathophysiology, and Treatments for MCS	Dr. Bill Meggs, East Carolina University School of Medicine
9:45 – 10:00	Break	
10:00 – 11:00	Sensitization in Chemical Intolerance and Gulf War Illnesses	Dr. Iris Bell, University of Arizona School of Medicine
11:00 – 11:30	Discussion	
11:30 – 12:30	Lunch	
12:30 – 2:00	Chronic Fatigue Syndrome: Research on the Occurrence, Definition, and Pathophysiology of CFS	Dr. William Reeves, U.S. Centers for Disease Control and Prevention
2:00 – 3:00	Fibromyalgia: An Overview of Research on the Diagnosis, Characteristics, and Pathophysiology of Fibromyalgia	Dr. Daniel Clauw, University of Michigan School of Medicine
3:00 – 3:15	Break	
3:15 – 4:15	Treatment Research on Multisymptom Illnesses; The Michigan Chronic Pain and Fatigue Research Program	Dr. Daniel Clauw, University of Michigan School of Medicine
4:15 – 5:00	Discussion	
5:00 – 5:30	Public Comment Period	
5:30	Adjourn for the day	

Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses
U.S. Department of Veterans Affairs
Lafayette Building, 811 Vermont Ave N.W. (Room 819) Washington, D.C.

Agenda
Thursday, April 7, 2005

7:30 – 8:00	Informal gathering, coffee	
8:00	Meeting called to order	Mr. Jim Binns, Chairman
8:00 – 9:30	Estimating Depleted Uranium Aerosol Doses and Risk: USACHPPM's Capstone Report	LTC Mark Melanson, USACHPPM Health Physics Ms. Mary Ann Parkhurst, Battelle Pacific Northwest National Laboratory
9:30 – 9:45	Overview of DU Research of Particular Relevance to Multisymptom Illnesses in Gulf War Veterans	Dr. Lea Steele, RAC-GWVI
9:45 – 10:00	Break	
10:00 – 10:45	Behavioral Changes and Brain Lipid Oxidation Following Uranium Exposure	Dr. Wayne Briner, University of Nebraska
10:45 – 11:30	Neurological and Behavioral Effects Following Co-exposure to Uranium and Stress	Dr. David Barber, University of Florida Center for Environmental and Human Toxicology
11:30 – 12:00	Discussion	
12:00 – 1:00	Lunch	
1:00 – 1:30	Gulf War Illness and Vaccines: An Overview of Issues and Epidemiological Findings	Dr. Lea Steele, RAC-GWVI
1:30 – 2:30	Evaluation of Adverse Events Following Anthrax Immunization	COL John Grabenstein, PhD Military Vaccine Agency, U.S. Army Medical Command
2:30 – 2:45	Break	
2:45 – 3:45	Health Effects of Receipt of Multiple Vaccines: Completed and Ongoing Studies	Dr. Phillip Pittman, U.S. Army Medical Research Institute of Infectious Diseases
3:45 – 4:30	Remaining Questions Relating to Immunizations Received by Gulf War Veterans	Dr. Beatrice Golomb, School of Medicine, Univ. of California at San Diego
4:30 – 5:00	Discussion	
5:00 – 5:30	Public Comment Period	
5:30	Adjourn for the day	

Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses
U.S. Department of Veterans Affairs
Lafayette Building, 811 Vermont Ave N.W. (Room 819) Washington, D.C.

Agenda
Friday, April 8, 2005

8:00 – 8:30	Informal gathering, coffee	
8:30	Meeting called to order	Mr. Jim Binns, Chairman
8:30 – 9:15	VA Office of Research and Development Update on Gulf War Illness-related Research Activities	Dr. Brian Schuster, VA Office of Research and Development
9:15 – 10:00	RAC-GWVI briefing and discussion with Secretary James Nicholson	
10:00 – 10:15	Break	
10:15 – 11:00	Discussion	
11:00 – 11:45	Highlights of Recently-Published Research Relevant to Gulf War Veterans' Illnesses	Dr. Beatrice Golomb, School of Medicine, Univ. of California at San Diego
11:45 – 12:30	Committee Business	Mr. Jim Binns Dr. Lea Steele
12:30 – 1:00	Public Comment Period	
1:00	Adjourn	

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 8:10 a.m.

Chairman Binns thanked the Committee members, speakers, and public for attending the meeting. He noted that there was a sign-in sheet for public comments scheduled for the end of the day.

Chairman Binns stated that Secretary Nicholson had scheduled time to meet with the Committee on Friday morning. However, due to his recent tenure as Ambassador to the Vatican, Secretary Nicholson had been asked to join the U.S. delegation attending Pope John Paul II's funeral, and so would not be participating in the Committee meeting.

Chairman Binns stated that the Committee's 2004 report and recommendations were intended to cover the first two years of the Committee's activities (2002-2003). He stated that there were a number of topics which were not addressed initially, but which the Committee was continuing to review. He gave examples such as: multisymptom illnesses that overlap with Gulf War illnesses (GWI), depleted uranium, vaccines, etc. He stated that the Committee would be preparing another report, which will address its work for 2004-2005.

As it was the beginning of a new year, he offered his assessment of where the Committee and its work stood. He stated that several things had been accomplished in the last year, including the production of an impressive report and the U.S. Department of Veterans Affair's (VA's) response to increase their funding for non-stress-related Gulf War illness research. He stated that, measured against the history of this subject and given the nature of government, this might be considered a significant accomplishment. On the other hand, he stated that he could not note any real research breakthroughs in the past year, and acknowledged that the GWI research funded by VA in 2004 was a "mixed bag." He stated that, by the terms of the Committee's charter, he would have to say that federal research had yet to make a difference in the health of ill Gulf veterans, and, at best, it could be said that people were pointed in the right direction.

This year, he stated that he hoped that a difference could be made. He noted that the key to this difference was not only offering general recommendations, but identifying specific, high-value research opportunities and putting them together in a coherent research plan to move towards really solving this problem.

He gave an example of such an opportunity. He noted that, on page 46 of the Committee's 2004 report, the Committee recommended that a Gulf War veteran brain bank be established. He stated that at the time this seemed a laudable goal, but rather general and long-term in nature. Recently, however, he was reminded of a conversation with Dr. Paul Greengard, 2000 Nobel Prize laureate, and Dr. Robert Haley, in which Dr. Greengard noted that one could learn a tremendous amount from "one good brain." Chairman Binns stated that this put things into a whole different context. He stated that, if "one good brain" could teach us a great deal, perhaps we should be turning VA upside down to find an ill veteran or two who are willing to provide this type of service to the future. He stated that he believed there were other high-value opportunities that could be pinpointed, and hoped everyone would focus on these as well.

Chairman Binns stated that, when the Committee first met three years ago, there was a real sense of urgency. He stated that he hoped this urgency could be rekindled. He stated that the Committee's work was not an academic exercise, and noted that 200,000 ill veterans were waiting for help.

Chairman Binns stated that the day's topic of discussion, i.e., the overlapping "civilian" diseases that share common elements with GWI, was very important. He stated that GWI researchers could learn from these illnesses, and, presumably, these researchers could learn from GWI research.

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

Dr. Steele suggested that the Committee members present introduce themselves to the audience, which they did. She introduced the Committee's staff: Ms. Laura Palmer and Ms. Barbara LaClair, the Committee's new Research Health Scientist.

Dr. Steele briefly explained the Committee's binder organization, and that members would find many of the papers being discussed inside. She noted that several general review papers were available for the public at the door.

CFS, Fibromyalgia, and MCS: Defined "Chronic Multisymptom Illnesses" in Relation to Gulf War Veterans' Illnesses

Lea Steele, PhD, Scientific Director, RAC-GWVI

Dr. Steele gave an overview of chronic multisymptom illnesses, e.g., chronic fatigue syndrome (CFS), multiple chemical sensitivity (MCS), and fibromyalgia (FM), and their relation to Gulf War veterans' illnesses. (See Appendix – Presentation 1.)

Chemical Sensitivity

William J. Meggs, MD, PhD, FACEP, FACMT
Chief, Division of Toxicology
East Carolina University School of Medicine

Dr. Steele introduced Dr. Meggs.

Dr. Meggs presented an overview of chemical sensitivity and the practice of environmental medicine in the United States. (See Appendix – Presentation 2.)

The meeting adjourned at 9:45 a.m. for a break.

The meeting reconvened at 10:03 p.m.

Time-Dependent Sensitization in Chemical Intolerance and Gulf War Illnesses

Iris R. Bell, MD, PhD
University of Arizona College of Medicine

Dr. Steele introduced Dr. Bell.

Dr. Bell presented an overview of neural sensitization in chemical intolerance (CI) and relevant findings in Gulf War veterans. (See Appendix – Presentation 3.)

Upon conclusion of her talk, Chairman Binns asked Dr. Bell for particular research suggestions in this field. Dr. Bell indicated that she would like to explore the possibilities of finding sensitizable individuals

prospectively, and to following their course with an exposure, in both a laboratory and field sense. She stated that she would also like to look at their dietary patterns and histories to see if there are connections with people experiencing CI. Dr. Bell indicated that other questions which needed to be answered were: (1) whether veterans with GWI can be tested for sensitization in the laboratory; (2) whether these veterans have CI, and (3) if so, what caused the elicitation of the sensitized reaction.

Mr. Joel Graves stated that Gulf veterans could be asked whether they had allergic reactions to things post-deployment that hadn't caused problems pre-deployment. He noted that, upon his return from the Gulf, he was severely allergic to his dog, which he had not been before his deployment. Dr. Bell stated that questionnaires had shown that new allergies were one of the changes reported by returning veterans. Dr. Meggs commented that the literature supported the concept that irritant exposures can potentiate the acquisition of IgE-mediated allergies to proteins. He noted that allergic rhinitis was historically a rarity in Japan; however, it became the most common immunological disease after the introduction of the diesel truck/car. Dr. Beatrice Golomb noted that the reaction to Mr. Graves' dog might actually have been to the flea collar or other pesticides on the animal. Dr. Bell stated that it was complicated to tease out a specific cause, and noted that there might also be synergistic effects between various agents.

Mr. Steve Robinson noted, anecdotally, that, while individuals who attended the National Gulf War Resource Center (NGWRC) conference were asked not to wear certain chemicals, the total number of individuals who were adversely affected was relatively low. He said that this correlated with some of the epidemiological data presented earlier in the meeting. Dr. Steele noted that sometimes people don't realize that they are sensitive, so it is difficult to get a handle on the extent of the problem.

Dr. Bell commented that the most sensitive individuals tend not to take the risk of going into public areas. She stated that many Gulf War veterans didn't see themselves as chemical sensitivity patients. However, when attempts are made to recruit Gulf War veterans in these studies, they are reluctant after finding out they are going to be exposed to low-level chemicals. She stated that this wasn't surprising, but noted that it does result in a biased sample.

Mr. Robinson asked whether an extended stay environmental unit was available in which these types of studies could be conducted. Dr. Bell stated that there were none in the United States. She stated that requests/suggestions had been made to build one, but funding was an issue. Dr. Meggs stated that there had been five government study groups that suggested creating a unit to study the effects of environmental exposures. However, no monies had been appropriated for its construction. Dr. Golomb noted her concern that such a unit could actually be free of all environmental contaminants. Dr. Bell acknowledged this problem, but stated that it would create a disparity between the ambient air and the exposure, allowing the effects of the exposure a chance to present.

Dr. Haley asked Dr. Bell for her suggestions on how to identify individuals with a propensity for sensitization. Dr. Bell indicated that the following criteria would help to identify individuals who were highly sensitive: family history of addiction, sucrose preference, and carbohydrate addiction scale. She stated that her group currently uses a chemical tolerance questionnaire, which includes a five-item screening scale to determine how ill the individual becomes from certain odors.

Dr. Bell noted that sensitization usually occurs in the short term in animals, particularly in sensitizable animals that react to novelty, but that only a subset of these animals have prolonged problems. She stated that this subset of animals can remain sensitized for up to a year without further exposure to the agent. Once the problem was set off, it was a big problem with no known way to reverse the condition. She noted that sensation seekers, i.e., those who need a high-stimulus environment, and the behaviorally inhibited/extremely socially shy seemed to be more sensitizable. She also noted that some

neurodegeneration research had indicated that shyness may be a factor in certain cases of Parkinson's disease.

Dr. Haley inquired about the source of the carbohydrate addiction scale, and whether it was a validated scale. Dr. Bell stated it was a scale published in a popular book on carbohydrates, which had been recommended to her by a fellow researcher. She acknowledged that there might be other scales, but this was the one known to her at the time.

In response to Dr. Golomb's concern about creating a perfectly chemical-free environment, Dr. Meggs commented that, while a perfect vacuum could not be created, vacuum research was still done. As such, he stated that this concern shouldn't be an impediment to doing environmental unit research.

Dr. Steele inquired whether there was a dichotomous or continuous distribution of sensitivity between the subgroups of symptomatic/non-symptomatic individuals. Dr. Bell stated it was probably a continuum. She stated that some people show this phenomenon regardless of the exposure intensity. She stated that determining the minimum threshold would be difficult. Dr Steele asked if the individuals who were severely ill were more likely to be sensitizable and vice-versa. Dr. Bell stated that in research on civilians, individuals who had made lifestyle changes to avoid certain exposures may be healthier than individuals who were chemically intolerant when tested in the laboratory.

Mr. Robinson stated that many Gulf War veterans had found "avoidance" as a treatment option through their own avenues. He stated that it did seem to work for them, but there is no scientific evidence that supports this approach.

Dr. Haley asked Dr. Bell to comment on the cellular neuroplasticity underlying this process and where research should go in this area. Dr. Bell stated that there had been some research regarding changes in RNA expression, but that she hadn't seen follow-up work. The research had focused on changes in receptors and dopamine release. She stated that some research had shown a change in the pituitary/adrenal axis in terms of response to stressors, which may modulate what happens in the response, but this hadn't been examined further.

Dr. Golomb stated that it might be interesting to investigate whether chemically sensitive individuals have an exaggerated oxidative injury marker. Dr. Bell agreed, noting a paper by Dr. Robert Paul at Washington University that indicated oxidative stress and the nitric oxide pathway might play a role. She stated that the question, though, was what part of the process researchers should begin examining.

Dr. Steele noted that there seemed to be a preponderance of MCS and CFS in women, and asked Dr. Bell about her comment regarding a possible protective effect of testosterone. Dr. Bell stated that there were two studies that showed removal of gonads did not make female animals any less sensitizable, while castration made male animals more sensitizable. She noted that testosterone would restore their resistance. Dr. Steele asked whether an exacerbation of chemical sensitivity was seen at certain times in the menstrual cycle. Dr. Bell stated that there was literature about olfactory sensitivity changes due to the menstrual cycle.

Chairman Binns asked Dr. Meggs to comment on the nasal inflammation hypothesis, and whether there was any evidence that this could be healed. Dr. Meggs stated that avoidance was the best way to improve a patient's functionality. He noted that an individual's symptoms could improve while in an environmental control unit, but that they weren't able to go back into their old environments, e.g. "sick building", etc. Chairman Binns asked if there were any other options besides avoidance. Dr. Meggs stated that he wasn't aware of any. He noted that, while high dose vitamin/anti-oxidant treatments were

being touted, there was little or mixed evidence proving efficacy. Dr. Bell stated that there was clinical evidence that there were some alternative medicine options, e.g., acupuncture, which could modulate the tendency to be sensitive. She noted that there was one study that suggested ginseng possibly could block sensitization, but she noted there was no follow-up work done on this.

Dr. Steele asked Drs. Bell and Meggs whether the literature indicated that once an animal was sensitized, it was always sensitized. Dr. Bell stated that there were many studies where all the animals were initially sensitized, but as time passed, fewer animals remained so. Dr. Meggs stated that the real key seemed to be patterns of exposure sensitizing an animal, noting that with removal of the exposure, the sensitization could be reduced over time.

Dr. Alan Fienberg, an audience member, noted that there was extensive research characterizing the biochemical mechanisms of dopamine and sensitization to drugs of abuse, e.g., cocaine. He stated that there was research that suggested these biochemical processes could be distinguished. Dr. Haley stated his belief that this was a research area to develop, i.e., how to bring human clinical models in parallel with intracellular models, allowing for testing of specific mechanisms in animal/cell models. He noted a recent neurodegenerative disease paper in the journal *Nature*, which showed a drug screening process that identified common antibiotics promoting, or increasing certain receptors in glutamate transport, that slowed the progression of ALS. Mr. Robinson asked if an antisense drug would have a similar result. Dr. Haley stated that they should come at it from a different angle, extending human studies as much as possible without creating any adverse consequences. He stated that the development of animal and/or cell models then could be developed to test every known drug or chemical. He stated that this approach seemed a promising option for this research area, and that there was a need to get various groups talking about these parallel research pathways.

Dr. Meggs commented that there were two distinct patient populations with neurotoxic exposures: those exposed to solvents and those exposed to organophosphates. He noted that a certain percentage of these populations develop chemical sensitivities. He stated that it was known that both of these classes of chemicals cause brain damage in high doses, and that there is neurogenic regulation of all of these mechanisms. He stated that those individuals exposed to low doses, who might have lesser damage, might not get better either.

Dr. Golomb commented on Mr. Robinson's comment about antisense agents. She indicated that, in light of Dr. Soreq's RNA expression research, it might be possible to develop these agents for treatment of CI patients.

Chairman Binns closed the discussion, noting that it had been stimulating and encouraged continued discussion about these ideas.

The meeting adjourned for lunch at 11:38 a.m.

The meeting reconvened at 12:35 p.m.

Chronic Fatigue Syndrome: Occurrence, Case Definition, and Pathophysiology

William C. Reeves, MD
Chief of the Viral Exanthems and Herpesvirus Branch, Division of Viral and Rickettsial Diseases
U.S. Centers for Disease Control and Prevention

Dr. Steele introduced Dr. Reeves.

Dr. Reeves gave an overview of chronic fatigue syndrome, including its prevalence, case definition, pathophysiology, and diagnosis. (See Appendix – Presentation 4.)

Dr. Steele asked Dr. Reeves to elaborate on the charge given to the statisticians with respect to looking for patterns in different data and seeing where these patterns overlap. Dr. Reeves said there were two questions being asked: Can we find patterns within the data? and, if so, Can we elucidate the pathway that is involved? He noted that this was one of the only genome projects trying to incorporate massive amounts of clinical data. The charge to statisticians was difficult because it involved analyses of disparate types of complex data such as information from EEGs and tests of behavioral/cognitive function. Dr. Golomb stated that it was important to look for these patterns, which would enable researchers to tease out and develop markers. Dr. Reeves stated that the U.S Centers for Disease Control and Prevention (CDC) would be more than happy to collaborate with the genomic researchers in this area.

Dr. Stephen Grate, an audience member, asked if the genomic or proteomic data were showing alterations/differences with respect to the duration of the illness. Dr. Reeves stated that these questions hadn't been examined yet. He noted that one of the "flaws" with current studies was that the individuals had been sick, on average, five years. He stated that CDC was working on three modeling studies. One study was with Emory University, evaluating the induction of CFS-like symptoms by therapeutic use of interferon alpha. Another study was being conducted with Australian researchers with respect to unexplained fatigue following infections, such as mononucleosis, Ross River virus and Q fever. Dr. Reeves noted that expression patterns in this study were predicting the individuals whose symptoms would not improve.

Dr. Meggs stated that this was an interesting technique and was different from how disease mechanisms were identified in the past. He asked, however, if it was clear that it would work for CFS. Dr. Reeves noted that early life stress changes the reaction of the hypothalamic-pituitary-adrenal (HPA) axis to similar stressors later in life. He stated that it was very clear that heart disease, breast cancer, and a variety of other cancers and chronic diseases have associations with early life stress. He stated this was probably due to a modification and alteration of HPA axis expression.

Dr. Meryl Nass, an audience member, asked Dr. Reeves if researchers were looking at infection titers, and whether a list of CDC's study parameters was available. Dr. Reeves stated that, in the clinical study, they did not look at titers. He stated that testing for possible infectious agents, including examination of titers and searches for latent DNA and 16S ribosomal RNA, had been conducted and published in previous articles. Dr. Nass asked about the findings of the Wichita study, and whether these were available. Dr. Reeves noted that the survey in Wichita was conducted between 1997-2000, with the in-patient study being conducted between 2000-2003. He stated that they were still working on the data. He noted that there were approximately 20 publications covering the findings of this study on the CDC website. He stated that a similar study was underway in Georgia.

Dr. Haley questioned the use of the HPA axis as the central model. He stated this was only one part of the story, and locked the researchers into the idea that childhood and emotional stress was the sole cause. He stated that there was a lot more evidence now that the neuroplasticity of other parts of the brain,

cytokines, neurotransmitters and dopamine, which aren't involved with the HPA axis, are more likely to be at issue. He stated that the use of the HPA axis as a central model was limiting. Dr. Reeves responded by saying: (1) the HPA axis model fits an established body of research that helps drive hypotheses, and (2) the HPA axis functions as a unit. He indicated that their research included studies involving functional MRI (fMRI), cognitive and stress measures, and evaluations of the immune system. He stated that these functions weren't unrelated to the HPA axis, and that it was an easy way to present the central hypothesis. He stated his belief that stress does play a role in this condition. He noted that stress wasn't simply abuse as a child, but included malnutrition, infections, injuries, living in poor environments, etc. He stated that CFS was a complex illness that did not have a single genetic or environmental cause.

Chairman Binns asked if Dr. Reeves had specific suggestions for applying this technology to Gulf War illnesses research. Dr. Reeves stated that the most productive route would be to focus on these types of illnesses surfacing from the current Gulf War, as individuals are "freshly ill." The studies should include population-based studies, to characterize the illness with standardized instruments and a clinical component. He noted that genomics and proteomics measures should also be utilized.

Chairman Binns asked for ideas with respect to study of illnesses from the first Gulf War. Dr. Reeves stated that similar types of studies should be done. He also noted that much of the question today for GWI is how to care for people who have been ill for 15 years. He stated that it was important to investigate the clinical parameters, how they could be measured, and how the patients' symptoms were improving or not improving over time.

Dr. Nass asked if the CDC study asked questions about problems following vaccines, and whether it would be possible to get a profile of vaccines given with respect to those surveyed from Warner Robins Air Force Base (Macon, GA). Dr. Reeves stated that this would be difficult within the structure of their population study. He stated that the study was being done as a random digit-dialed survey of the population.

Dr. Steele asked Dr. Reeves why he questioned the use of case-control studies in this area of research. Dr. Reeves stated that case-control studies were good for simplistic things, but more than a single association of a risk factor or symptom was needed in cases like this. Dr. Haley agreed that simple case-control studies weren't enough, but that mechanistic measurements were needed and that this should progress to animal models. Dr. Reeves noted that defining the case groups in CFS and GWI studies was difficult, due to competing comorbidities.

Chairman Binns thanked Dr. Reeves.

The Pathophysiological Basis of Fibromyalgia

Daniel J. Clauw, MD
Professor of Medicine and Director, Chronic Pain and Fatigue Research Center
University of Michigan Medical Center

Dr. Steele introduced Dr. Clauw.

Dr. Clauw gave an overview of current research on the nature and causes of fibromyalgia (FM), and relevant studies related to Gulf War illnesses. (See Appendix – Presentation 5.)

Dr. Meggs asked Dr. Clauw what he thought might be the neuroanatomical cause of the "seesaw effect" happening in the insula portion of the brain. Dr. Clauw indicated it might be a preponderance of specific neurotransmitters or neuronal imbalance. He stated that many in this field view pain as being a form of low-grade epilepsy, i.e., the brain is hyperactive. He noted that many of the drugs used in this field are ones that raise the levels of inhibitory neurotransmitters.

Dr. Golomb commented that one had to be careful focusing on commonalities in multisymptom conditions and noted the need to look at both the similarities and differences. She noted Dr. Clauw's observation that Gulf War veterans do not experience the same response to tender point pressure, which might suggest there was a different mechanism in these ill veterans. She also noted their fMRI findings, which showed certain areas "lit up" specifically in the non-Gulf War FM patients, but not the Gulf War veterans, and vice versa. Dr. Clauw agreed with her with respect to their fMRI findings, but noted that the FM case definition might account for the tender point differences.

Chairman Binns asked if Dr. Clauw would include chemicals as a "stressor." Dr. Clauw stated he would, and in certain individuals, chemicals were major stressors.

Dr. Nass expressed her interest in the "turning up the volume" theory. She noted her own patients' accounts of being overstimulated when they were in large groups.

Dr. Jack Melling asked Dr. Clauw to expound on the triggers of FM, i.e., what causes someone to go from normal range to being a FM patient. Dr. Clauw stated that his group currently was conducting longitudinal studies and trying to identify the mechanisms for increased sensitivity to pain. He noted that studies of exercise deprivation had shown emergence of pain problems in some individuals.

Dr. Haley asked if quantitative temperature sensitivity had been considered in FM studies. Dr. Clauw indicated this had been examined, and there was a similar shift "to the left." He stated that there was considerable activity observed in fMRI in response to touch.

Dr. Steele asked if studies had shown that sleep deprivation, not just exercise deprivation, caused an increase in pain. Dr. Clauw indicated that early studies suggested that lack of sleep was the cause of FM. He stated this was way too simplistic, but likely played a role. Dr. Steele asked how the central pain processing explanation of FM ties in with the other symptoms of FM, e.g. gastrointestinal, sleep abnormalities, etc. Dr. Clauw stated that sensory and pain-processing abnormalities, along with dysautonomia, probably do explain most of the symptoms of FM. Chairman Binns noted that he had heard from FM patients that they couldn't sleep because their mind was "racing" or couldn't be "turned off."

Mr. Robinson asked if Dr. Clauw knew how many first Gulf War veterans had been diagnosed with FM. Dr. Clauw stated he didn't, and noted that some veterans were resistant to being diagnosed with FM

because it would affect their disability benefits. He also stated that because the VA historically had cared primarily for men, the premiere FM researchers haven't focused their research in the VA environment. He noted that FM patients were managed poorly most everywhere, but that more attention is given to it now. Mr. Robinson agreed, and stated that VA didn't cover most treatments that veterans were seeking. He stated that when the disability benefit law was passed, many veterans sought an "undiagnosed illnesses" classification. He stated it would be interesting to know how many of the deployed veterans who filed claims for undiagnosed illness would fit the criteria for FM.

Dr. Melling asked if Dr. Clauw found the words "stress" and "stressors" to be viewed so negatively by patients that they are difficult to use in discussion of chronic multisymptom illnesses. He stated that most present understood the meaning of "stressors" and "stress" and that this differs from the meaning used by the general public. He noted this was a problem, at least a perception problem. Dr. Clauw agreed and stated he doesn't use the term "stress" unless he has time to explain its meaning. Ms. Marguerite Knox noted that this is how medicine is currently divided: mental health and acute care. Dr. Clauw stated that the problem with this approach for these illnesses is that no one has "ownership." He noted the VA's survey of its own physicians where 75% of the psychiatrists believed GWI was a medical problem, while 75% of the internists believed it was a psychiatric problem. He stated that it was fascinating that clear psychiatric diseases, such as schizophrenia, have greater acceptance than FM, CFS, GWI, and MCS. He noted these diseases were "left behind" because there was no subspecialty group or effective advocacy group to bring them into the mainstream. He noted that FM had come a long way in the last 10 years, due to researchers' ability to study pain objectively, along with pharmaceutical interest in this area.

Ms. Julia Dyckman, retired Navy captain and audience member, asked Dr. Clauw if the problems with the autonomic nervous system were due to dysfunction or failure. Dr. Clauw stated that this was subtle dysfunction. He characterized it as an instability or dysregulation of the autonomic nervous system.

The meeting adjourned for a break at 3:20 p.m.

The meeting reconvened at 3:30 p.m.

Treatment of Fibromyalgia and Other Chronic Multisymptom Illnesses

Daniel J. Clauw, MD
Professor of Medicine and Director, Chronic Pain and Fatigue Research Center
University of Michigan Medical Center

Dr. Clauw gave a presentation about research on treatments for FM and other chronic multisymptom illnesses. (See Appendix – Presentation 6.)

In his discussion of pharmacological compounds under development, Dr. Clauw disclosed a financial interest in the company that manufactures Milnacipran. He noted that if the VA wished to do clinical trials for FM, Duloxetine was one drug that could be studied. He stated that the VA should be able to get a drug company to provide their product for a combined therapy trial, such as drug and cognitive behavioral therapy (CBT).

Dr. Meggs noted that, anecdotally, there seemed to be a relationship between FM and later onset rheumatoid arthritis and other autoimmune diseases. Dr. Clauw stated that he hadn't seen this in his practice. He stated that these illnesses are common in the population, and epidemiological studies were not showing such a relationship.

Ms. Alison Johnson, an audience member, noted that tricyclic drugs didn't seem to work with MCS patients. Dr. Clauw stated that he has had some success when he starts his chemically-sensitive FM patients on very low doses of tricyclics.

Mr. Robinson asked if there was evidence that rolfing worked for FM patients. Dr. Clauw stated that there weren't data to support either way, but that he does recommend it to some patients.

Dr. Bell noted that the reactions seen in chemically sensitive individuals taking tricyclics may be seen as an amplification or sensitization process, with respect to the noxious threshold for these patients. She noted that there was one study that indicated electroacupunture did provide some relief to FM patients. She noted that she was intrigued by the benefits and parallels with respect to combination therapy findings between FM patients and chemically sensitive patients. Dr. Clauw agreed, and noted that treatment of these patients required finesse.

Dr. Haley asked if the drug hypersensitivity in these patients had been well researched to determine whether they had intrinsic hyperresponses, or whether there were issues involved in elimination of the drug. Dr. Clauw stated that a research group in which he was involved 8-10 years ago had determined that it wasn't a problem with accumulation or toxicity of the drug. He noted that it seemed patients were more sensitive to the neuroactive drugs. He further noted that this sensitivity didn't apply to all drugs, but rather to specific classes.

Dr. Steele asked about Dr. Clauw's registry of screened and available research subjects. He stated that they had established a registry at the University of Michigan. The registry was not intended itself for research, but provides researchers with a streamlined recruitment process and made subjects available for future studies, such as those involving genomics or proteomics. He stated that it wasn't as easy for them to attract a large study population as the CDC does. Dr. Haley stated that clinical studies, not population studies, were better for mechanistic studies.

Dr. Steele noted that ill veterans frequently contacted the Committee and its members about being a part of research studies. Dr. Clauw stated that these patients could be referred to him. He indicated that it had been difficult to find Gulf War veterans previously, but that they would love to develop a Gulf War cohort available for study.

Chairman Binns asked if Dr. Clauw had found in his clinical practice that some patients' problems started with chemical exposure. Dr. Clauw stated that it was terrible for a patient to think they had been "poisoned." He provided three examples from his career, and indicated that those patients who felt they were victims did not fare as well as those who acknowledged their problem and moved on. He indicated that he thought toxins played a role in the illnesses experienced by some Gulf War veterans, but that it was destructive to their health for them to think that they were poisoned. He indicated that this reinforced the patients' victim mentality, and took away their sense of control over the situation. He indicated that these patients tended to become passive and feel helpless in finding ways to improve their health.

Dr. Melling stated that he agreed with Dr. Clauw's analysis about the need to avoid the victim mentality. He noted, however, that the Committee faced a dichotomy of charges. He stated that, on one hand, the Committee was trying to understand Gulf War illness and the various treatment options. On the other hand, it was also trying to prevent future occurrences by determining the cause or causes of these illnesses. He agreed that, for an individual patient, the best thing was to "move on." However, for the system as a whole, the Committee must also look towards prevention. Dr. Clauw stated that he wasn't trying to criticize the Committee, but that the effect on patients who develop this belief was very real.

Mr. Robinson agreed that Dr. Clauw's point was good. He noted, however, that Gulf War veterans were just getting to the point where they could stop thinking of themselves as victims, given recent scientific advancements. He stated that it was important for the veterans to be "victims" in the beginning, because the Government refused to acknowledge that their Gulf War service had any bearing on their illnesses. He stated that this acknowledgement now allowed the focus to move to positive, proactive treatments and therapies.

Chairman Binns asked Dr. Clauw to explain the relationship between autonomic nervous system dysregulation and the pathway addressed by the drugs he had discussed. Dr. Clauw stated that most of the drugs worked on serotonin and norepinephrine, which are neurotransmitters at the epicenter of the autonomic nervous system. Chairman Binns asked whether this meant that the autonomic dysfunction was the core problem, but that therapy tended to ameliorate it. Dr. Clauw agreed it was a problem and, if addressed, it made at least a subset of individuals better.

Mr. Graves asked if FM patients experienced a higher incidence of low-impact injuries. Dr. Clauw stated that they did. He stated that earlier in their lives, the patients might have thought they were injured more than others, when it also might be that their lower pain thresholds lead to more symptoms.

With respect to the "victim" mentality, Dr. Meggs stated that it must be acknowledged that individuals do develop chronic disabilities from toxin exposure. However, he noted that the most destructive thing to the patient's health was having pending litigation that encouraged continued disability in order to achieve settlement. Dr. Clauw agreed that it was a terrible thing to have a link between proving one's disability and receiving clinical care. Mr. Steve Smithson pointed out that the VA system was based on this causal connection, i.e., the veteran must show that their illness was service connected before they could qualify for treatment. He stated that the veteran wanted to get better, but unless he or she can show what caused the condition, they aren't eligible for treatment. He said it is easy to say: "Don't worry about what causes it. Move on." But the system puts the veteran in a catch-22, which must be considered when discussing these veterans' treatments or benefits. Dr. Golomb agreed that, based on her clinical practice, patients with pending litigation did less well.

Ms. Denise Nichols, a Gulf War veteran and audience member, agreed that the adversarial process did interfere with patient care. She stated that there had to be a trust mechanism between the patient and health care provider. She noted that there was a loss of trust when the government denied a connection between the veterans' service and illnesses. She stated that the goal wasn't to find a "golden egg", but to find out the truth.

Dr. Steele asked Dr. Clauw about his thoughts about Ampligen. Dr. Clauw declined to discuss this.

Ms. Julia Dyckman asked Dr. Clauw for his thoughts about chronic pain clinics and their coordination. Dr. Clauw stated that there was no standardization for chronic pain clinics. He stated that VA wasn't any worse at providing this type of care than private pain clinics. He stated that many pain clinics have become "opiate clinics," despite findings that opiates provide little or no benefit for central nervous system dysregulation. He stated that many of the good academic pain clinics had to close because they were losing money.

Chairman Binns asked if Dr. Clauw's patients represented a broad range of severity, e.g., from very incapacitated to those who function in a moderate way, and how this related to their improvement. Dr. Clauw stated that he could help the majority of FM patients that wanted to get better. He noted that he couldn't make them "well" or symptom-free. However, with a combination of drug and non-drug therapies, he stated that these patients could get better. Dr. Clauw indicated that changes in treatment

programs at VA could make it possible to improve veterans' health care and reduce the need for disability compensation. He noted problems faced by researchers in establishing CBT programs for the clinical trials, and the reasons behind the disparity in their operation/results. Dr. Haley asked how much these types of programs (CBT) would cost. Dr. Clauw indicated that they wouldn't be very expensive.

Dr. Steele noted that, at a previous Committee meeting, Dr. Charles Engel had presented data that patients in CBT programs didn't do much better, on average, than those who didn't receive therapy. Dr. Clauw stated that he believed CBT wasn't sufficient by itself, and that it must be combined with a symptom-based pharmacological approach to help people get over the initial hurdles. Dr. Golomb asked if there were combination CBT and drug trials that reflected this finding. Dr. Clauw stated that it was well-documented in depression studies, but not for pain. He noted that there wasn't a specialized funding authority for pain research, and that pharmaceutical companies weren't interested in funding combination trials.

Ms. Venus Val-Hammack, a Gulf War veteran and audience member, stated that there were no VA medical center clinics, at least in the Northeast United States, that would evaluate a veteran for these chronic multisymptom illnesses. Dr. Clauw stated that the veteran patient needed to find an empathetic physician who was willing to work and learn with him or her. He stated that every subspeciality was trying to avoid this group of patients due to the time expenditure required. His group had set up a program at the University of Michigan to educate physicians in this type of care.

Mr. Robinson asked if Dr. Clauw had submitted information on FM for inclusion in the Veteran's Health Initiative (VHI) series on Gulf War veterans. Dr. Clauw stated that he was a member of the panel that established the VA/Department of Defense (DoD) practice guidelines for medically unexplained symptoms. He stated that, unfortunately, most physicians weren't using them, partially due to lack of knowledge of their existence. He stated that the guidelines were good, but could be improved with background information about FM, explaining underlying processes and why a patient is treated in a particular manner. He stated that in his clinic they have a "Top 10" list of advice for FM patients. The list is brutally honest, and helps because it can be diifficult at times for the physician to explain these issues to a patient directly.

Dr. Bell commented that there were emerging themes relating to treatments from the field of alternative medicine. She stated that randomized controlled trials were difficult because many of the patients were trying various, and sometimes bizarre, treatment combinations.

Dr. Steele commented that the large-scale exercise and behavioral therapy (EBT) clinical trial was conducted on Gulf War veterans without preliminary work to determine the best study design and application of treatment. Dr. Clauw stated that much was learned from this study, i.e., what to do and also what not to do. Dr. Steele noted that the same approach was applied with the large-scale VA antibiotic clinical trial study. Dr. Clauw indicated that there was a push by Congress to get this study done. He stated that the VA was in a position to take the next good step in combination treatment trial studies.

Dr. Steele asked if the researchers in this group, including Dr. Clauw, had learned how to improve upon the study's design, and how EBT might best be used to treat Gulf War veterans. Dr. Clauw stated that there were several problems with the EBT study, e.g., new CBT programs and practitioners and lack of a specialized GWI patient education program that explained the illnesses and how or why the treatment would work. Dr. Steele asked whether Dr. Clauw believed that even if CBT was performed well, pharmaceutical treatment was still needed. Dr. Clauw said that he believed that to be true.

Public Comment – Day 1

Chairman Binns opened the floor to public comment.

Ms. Alison Johnson spoke to the Committee. She commented that few within VA understood MCS. She stated that there was a need for environmentally controlled research units. However, she didn't think VA was in a position to do this type of study. She stated that the success of this type of study most likely depended on nongovernmental funding. She stated that before this funding could be secured, scientific support was needed. She suggested that the Committee make a recommendation with regards to the construction of such a unit for GWI study.

Ms. Denise Nichols spoke to the Committee. She stressed the need for research coordination and improved communication with veterans about ongoing VA clinical trials in which they might be eligible to participate. She commented that the veterans needed to see results from this effort, and the establishment of a Gulf War veteran brain bank would be helpful. She suggested that information concerning research funding and proposal submission deadlines be placed on the Committee's website. Dr. Steele indicated that this was already being planned, starting with the recently announced VA request for proposals (RFP) for Gulf War illness research.

Mr. Robinson asked Dr. O'Donnell, an audience member who works for DoD's Deployment Health Support Directorate, whether the Deploymentlink website (http://www.deploymentlink.osd.mil/) had a medsearch capability to list current DoD clinical trials. Dr. O'Donnell stated that it did not. He stated that it only provided information about past clinical trials.

Ms. Val-Hammack spoke to the Committee and Dr. O'Donnell about the need to update the VA/DoD clinical practice guidelines on VA and DoD's websites.

Chairman Binns thanked the meeting's participants for attending. He stated that this was an example of what these meetings could be at their best. He noted that much was learned and misunderstandings addressed quickly when individuals were brought together into one room.

The meeting adjourned for the day at 5:30 p.m.

The meeting reconvened Thursday, April 7, 2005, at 8:12 a.m. Ms. Marguerite Knox was not able to be present for this day's proceedings.

Depleted Uranium CAPSTONE Aerosols Study and Human Health Risk Assessment

LTC Mark A Melanson, PhD, CHP
Program Manager, Health Physics
U.S. Army Center for Health Promotion and Preventive Medicine

LTC Melanson gave introductory remarks and provided context for DoD's Depleted Uranium Capstone Aerosols Study and Human Health Risk Assessment project. (See Appendix – Presentation 7.)

Estimating Depleted Uranium Aerosol Doses and Risks: An Overview of the Capstone Depleted Uranium Aerosol Study and the Capstone Human Health Risk Assessment

Mary Ann Parkhurst, MS
Principal Investigator, Capstone Depleted Uranium Aerosol Study
Battelle/Pacific Northwest National Laboratory, Richland, Washington

Ms. Parkhurst presented an overview of the findings of the Depleted Uranium Capstone Aerosols Study and Human Health Risk Assessment project. (See Appedix – Presentation 8.)

Dr. Haley asked why depleted uranium (DU) had fewer or less severe health side effects than generic alpha emitters. Ms. Parkhurst stated there were many human studies relating to uranium exposure, which found no increase in cancer rates. She stated that the report's Human Health Risk Assessment examined this evidence. She stated that they were unable to say there was no risk, but that no adverse outcomes had been observed yet.

Dr. Haley asked about the meaning of the term "Capstone." LTC Melanson stated that a capstone was a crowning closure on a building. He stated, from the DoD's perspective, this report was the deciding or crowning study for modeling DU aerosol concentration inside a vehicle hit by DU munitions.

Mr. Robinson asked whether any DU armored vehicle had been penetrated. LTC Melanson indicated that DU armor was located only in a couple classified locations on the vehicle, and these sections had not been breached. Dr. Steele asked whether any DU munitions had penetrated DU armor. LTC Melanson indicated that none had.

Mr. Robinson asked whether any of the 1700 DoD personnel tested for depleted uranium were Gulf War veterans. (See Slide 11 of Presentation 7.) LTC Melanson stated that these were individuals who served in Operation Iraqi Freedom (OIF). Mr. Robinson asked whether there was urine testing data for veterans who served in the first Gulf War. LTC Melanson stated that he did not have good data for these veterans. Mr. Robinson stated that the U.S. Government Accountability Office (GAO) investigated whether returning OIF veterans were being screened for depleted uranium upon request, and found poor compliance. He asked if compliance had been improved. He also asked whether the test being utilized was sensitive enough. LTC Melanson stated that, per DoD policy, personnel with Level 1 and 2 exposures were to be tested for depleted uranium. He acknowledged that there had been concerns about whether the 442nd Military Police (MP) Unit had received this testing. He stated that, per DoD policy, personnel with Level 3 exposures who requested testing were also to be tested.

Mr. Robinson stated that there had been problems with screening 442nd Unit personnel, and once tested, issues arose as to whether the test was sensitive enough. LTC Melanson stated that one of the methodological challenges of depleted uranium testing was background uranium levels. He stated that this then raised concerns about the level at which health effects occurred. He stated that the test used by DoD (inductively coupled plasma mass spectrometry) was sensitive enough to detect DU levels 100 times below those levels that cause concern. He reviewed the situation involving the 442nd MP Unit. He stated that those who had requested testing had been screened, but that there had been a delay with their test results. He stated that the soldiers then had contacted the NY Daily News, who provided alternative testing by the Uranium Medical Research Center (UMRC). He stated that the UMRC test results reported only that depleted uranium was present but did not report the actual quantity, which was fundamental in clinical laboratory analysis. He also expressed concern that the laboratory that performed the analyses was a geochemistry laboratory, and not an accredited clinical laboratory for testing of human specimens. He noted that the U.S. Army Center for Health Promotion and Preventive Medicine (USACHPPM) laboratory is accredited, as are the U.S. Armed Forces Institute of Pathology (AFIP) and CDC laboratories, which are also used for depleted uranium testing of returning OIF personnel. He stated that he also had no knowledge of the quality control data for the UMRC laboratory, and therefore it was difficult to comment on the accuracy of their results. He stated that duplicate testing was conducted in another accredited laboratory, which verified the USACHPPM results for the 442nd MP Unit personnel. He stated that the levels of depleted uranium found in the 442nd MP Unit personnel were comparable to the background levels of uranium found in the general population, and therefore didn't show an overexposure to depleted uranium.

Mr. Smithson asked what percentage of the 1700 DoD personnel screened had received Level 1 or Level 2 exposures. LTC Melanson replied that it was hard to stratify the results in this manner. He stated that the exposure information came from self-reported questionnaires, which the testing laboratories did not always have, and when they did, the solider did not always identify their exposure level, e.g., being involved in a friendly fire incident. Mr. Smithson asked how many friendly fire incidents had occurred in the current conflict, and whether this was documented separately from the self-reported questionnaire data. LTC Melanson stated that there had been fewer friendly fire incidents in OIF during the initial major combat operations with Iraqi forces, but he did not know the exact number.

Mr. Robinson asked whether there was an automatic process for battlefield exposure (Level I, II, or III) to be reported upon evacuation from the region, and whether this generated an automatic screening for depleted uranium. LTC Melanson stated that when a soldier was wounded, this individual was flagged as having potential Level 1 exposure. He stated that they couldn't guarantee 100% that every individual was being tested, but that the current policy was helping to test the majority of those exposed. He noted that most of the 1700 individuals tested had Level 3 exposures.

Mr. Robinson asked: (1) why protective measures regarding depleted uranium weren't being taught to soldiers in basic training; and (2) what protective measures were taken by Capstone personnel during the model testing. LTC Melanson stated that, based upon the conclusions of the Capstone report, he did not believe additional precautions were necessary as the radiologic and chemical risks were not significant, especially in comparison with other combat risks. He stated that the U.S. Army Medical Department still needed to make this determination. He did note that training should include advice about making sure the tank ventilation system was operating. In terms of additional protective recommendations, he indicated that there was the need to balance the risk of protection versus the risk of operational degradation. He stated, based upon the findings of the Capstone report, the risks were low.

With respect to the protective measures taken by Capstone personnel, he stated that these experiments were in a controlled peacetime environment versus the uncertain, active battlefield, and that OSHA

regulations were applicable in this situation. Mr. Robinson asked if there was a middle ground approach to training. LTC Melanson noted that there was basic instruction, e.g., don't pick up penetrators. Mr. Robinson asked if the technical manual, which covered safety standards for extraction of individuals from vehicles struck by DU, was no longer applicable based upon the Capstone findings. LTC Melanson stated that the technical manual was written without this information and should be reviewed.

Dr. Meggs asked the Committee and LTC Melanson if they thought DU played a role in the chronic multisymptomatic diseases evidenced in 150,000 Gulf War veterans, and whether the Committee should continue pursuing this as a causal factor for these illnesses. Dr. Steele stated that the rest of the morning's speakers would address possible biological mechanisms relating to DU exposure to GWI.

Dr. Haley asked what was known from the Capstone report about DU resuspension and the long-term civilian exposure to DU. LTC Melanson stated that this report did not address this question, but there was a simple qualitative experiment that would demonstrate the relative risk of the initial aerosol produced versus resuspension. He stated that the highest concentration of localized DU fall-out occurred at the time of penetration and that the DU settles close to the vehicle. He went on to discuss his work in the Balkans with the UN to study the environmental effects of DU. He stated that the conclusion of all three Balkan missions was that the primary pathway of concern for the local population was via groundwater. He noted that many rounds fired in the Balkans were lodged beneath the ground. He stated further research was needed in this area to consider possible effects 10, 100, etc., years from now, taking into consideration the prewar levels of uranium found within the soil.

Dr. Haley asked if the DU amounts deposited in the Balkans would significantly increase the exposures. LTC Melanson stated that modeling was being conducted at three test ranges in Maryland, Arizona, and Indiana. Results at these sites had found little widespread migration and uptake of uranium into the soil. The challenge was comparing the geology of these test ranges with Bosnia, Kosovo and Iraq. He stated that the National Atomic Energy Agency was conducting sampling in areas of Kuwait where DU was fired, and water sampling was being conducted near attack locations in the Balkans. Tests had found only one case of detectable levels of DU in the groundwater, and it was below the World Health Organization's limits for uranium in drinking water. He stated that, quantitatively, he didn't think DU was a big problem, but that there were questions remaining as to how best to conduct environmental monitoring.

Chairman Binns thanked LTC Melanson and Ms. Parkhurst.

The meeting adjourned for a break at 9:53 a.m.

The meeting reconvened at 10:10 a.m.

Research on Health Effects of DU in Relation to Gulf War Veterans' Illnesses

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

Dr. Steele presented an overview of research findings and remaining unanswered questions pertaining to DU's relationship to Gulf War veterans' multisymptom illnesses. (See Appendix – Presentation 9.)

Dr. Steele noted that the Capstone Report provided exposure measures, which had been lacking, for individuals inside tanks hit by DU munitions.

Behavioral Changes and Brain Lipid Oxidation Following Uranium Exposure

Wayne Briner, PhD
Professor, University of Nebraska at Kearney

Dr. Briner presented his research findings pertaining to DU's behavioral effects on adult and developing mice, along with his findings pertaining to brain lipid oxidation levels in adult rats following exposure to uranium. (See Appendix – Presentation 10.)

Dr. Meggs asked why Dr. Briner had used uranium acetate, and how it compared to the DU used in the battlefield. Dr. Briner stated that DU oxide was used primarily for tank shells. He stated that they used uranium acetate because it is easily available and soluble in water.

Dr. Golomb asked if other studies had shown that DU could cross the blood-brain barrier. Dr. Briner indicated that there were other studies supporting this.

Chairman Binns asked whether the amount of uranium to which the mice were exposed was relatively large or small. Dr. Briner stated that, in order to do comparisons, aerosol modeling was needed to determine human exposure over a period of time.

Dr. Haley asked if these findings resembled those for lead and other heavy metals. Dr. Briner stated other heavy metals were oxidizers, e.g., aluminum, iron, copper, zinc, etc. He stated that he was the first to look at lipid oxidation in this manner.

Chairman Binns thanked Dr. Briner.

Neurological Effects of Acute Uranium Exposure

David Barber, PhD
Assistant Professor, University of Florida

Dr. Steele introduced Dr. Barber.

Dr Barber presented his group's findings regarding the neurological effects of acute uranium exposure. (See Appendix – Presentation 11.) He stated that they believed that uranyl acetate was representative of the same transport mechanisms as other uranium exposures, because once dissolved in the blood, it was in the form of a uranyl ion, usually uranyl carbonate.

Mr. Graves asked what was known about the long-term effects of uranium in the human body. He noted that Dr. Briner had indicated the pulmonary half-life of uranium was four years. He asked what was known about neurological damage, and whether this damage was permanent or if there was a natural recovery as time passed. Dr. Barber stated that it depended on the plasma concentration and the amount that had gotten into the brain. He stated that large quantities of uranium wouldn't cross over into the brain unless there was a spike in plasma levels. He stated that at some point, a steady state would be achieved, i.e., the amount of uranium going in and out of the brain was balanced. He stated that this steady state level of uranium depended on the level of exposure and where it binds. He wasn't sure if their current studies would directly address this question, because questions about long-term effects couldn't be answered in thirty days after a single exposure. He stated that they were doing a six-month study, but it involved continuous exposure. He stated, though, that studies could be done to address Mr. Graves' question.

Mr. Graves asked if Dr. Barber planned on looking at the myelin sheath and whether uranium was present in this region. Dr. Barber stated that they could look at the ultrastructure of the myelin sheath to see if there was disruption. He noted that, as uranium is very dense, it might be possible to see if uranium was deposited in the sheath. Mr. Graves asked whether the damage would be permanent if the uranium made its way into the myelin sheath. Dr. Barber stated that it was clear that their administration of uranium caused an adverse neurological effect, but it wasn't clear how long this effect would last or why it happens. He stated that it didn't appear to be structural, at least at the gross level. He stated that closer study was needed and possible, but would be difficult with low-level functional insults.

Dr. Steele asked Dr. Barber to draw parallels between his findings and what was known about other metals. Dr. Barber stated that uranium was very similar in its distribution to other divalent metals, e.g., lead, manganese, calcium, etc. He stated divalent metals tend to go to the same locations in the body, through similar carrier mechanisms. He stated that there were probably specific uptake mechanisms that are similar, e.g., uranium binds to transferrin to cross the blood-brain barrier.

Dr. Golomb stated that there was one study which found that aluminum lead to leakiness of the blood-brain barrier. She stated that, even though they hadn't seen stress-enhanced entry of DU, it would be interesting to know if DU enhanced the potential entry of other substances. She noted that this possibility had been studied for other substances using virulent/non-virulent viruses. Dr. Barber stated this was an interesting idea and the study was possible, but noted that, with uranium, it would be hard to tease out the confounding effects of uremia.

Mr. Robinson asked if Dr. Barber found the different exposure classifications (Level I-III) helpful in doing his research. Dr. Barber stated that the single-exposure, 30-day, experiment could be considered a lower limit, while the six-month continual exposure experiment would be an upper limit. He stated that, at the end of their current study, they hoped to have data on plasma and kidney concentrations, and how these concentrations relate to brain concentrations and effects. He hoped that these data could then be used to develop a model that helps assess risk for various levels of exposure.

Chairman Binns thanked Dr. Barber, and opened the floor to discussion about the previous two presentations.

Mr. Graves commented that there was a population of soldiers who were exposed to a cocktail of toxins while driving through areas littered with burning vehicles, which had been shot with DU munitions, in Iraq. Dr. Barber stated that combinations/mixtures were a challenge for toxicologists and that it was difficult to test beyond a binary mixture. He stated it was virtually impossible to test this specific combination, but tests could be done to determine if it was a possibility that the combination could cause problems.

Mr. Robinson noted that blood was drawn before soldiers deployed in the first Gulf War, which hadn't been screened yet. He also noted the Committee's discussion about establishing a Gulf War veteran brain tissue bank. He asked if these brain tissues and blood samples would help in Dr. Barber's study, despite being fourteen years after the exposure. Dr. Barber stated that the analyses could be done to determine if uranium levels were still elevated. If they were, they could try to correlate the results to the type of brain levels seen in his group's research studies. However, without knowledge of the soldier's specific exposures, he stated it would be difficult to interpret negative results.

Dr. Steele asked if there were scenarios with other metals, in which the substance had been present but dissipated, leaving permanent damage. Dr. Barber cited methyl mercury, in which neuronal loss and

gliosis led to permanent damage/deficit. He stated that they hadn't seen this yet with a single dose of uranium, but acknowledged the possibility of this paradigm.

Dr. Golomb noted that, in light of the information about lipid oxidation and possible oxidative injury, there could be a neurodegenerative process occurring. Dr. Barber agreed, and hoped that in their six-month study, they could address this issue directly. He stated that they had looked at glutathione levels, and didn't see any differences in totals or in ratios of oxidized to reduced, an indirect marker of lipid peroxidation. Dr. Barber stated that the uranium might be in a depot that is exchanged very slowly, but it is unclear what it is bound to. He stated that they planned to do uranium affinity studies to determine this.

Dr. Steele noted that solubility played a major role in DU's effect on renal toxicity and how uranium is transported to target organs. She asked if one of the speakers could elaborate on how the different uranium forms become soluble in the blood. Mr. David Alberth, a senior health physicist with USACHPPM, stated that modeling of uranium solubility in the lung was done in the Capstone study, and that Lovelace Respiratory Institute had conducted simulated lung fluid studies for DoD. Going back to basic toxicology, the amount that enters the blood stream is most important. If the substance is highly insoluble, it would take longer to get into the blood stream than less soluble substances. Highly insoluble substances that were ingested were pretty much gone from the system within 24-72 hours. He indicated that the National Council on Radiation Protection Measurements was working on a wound/injection model for the introduction of uranium into the body, and a report on this was undergoing peer review.

Dr. Steele asked if the uranium inhaled in the tank scenarios was moderately soluble. Ms. Parkhurst provided a brief overview of dose calculations and solubility. She stated that, under the ICRP-66 model, the uranium was considered a Type M, i.e., very soluble at first with a slow decline. However, using the ICRP-30 model, the uranium was considered a Class Y, i.e., taking years to dissolve.

Mr. Robinson asked about the maximum/minimum particulate size that is respirable and could be retained in the lung. Ms. Parkhurst said that particles less than 5 microns were able to reach the alveoli. She stated that 10 microns had been the conventionally accepted number, but that this was larger than most particles that would get into the lung. Mr. Alberth stated that the Capstone researchers had looked at particles that were less than 1micron, 1-5 microns, 5-10 microns, and 10-100 microns. He said that they were concerned about the respiratory aspects, and how this affected the physiological model of where different particle sizes reached. Ms. Parkhurst stated they had found that the smallest particles were the least soluble, where typically they were expected to be the most soluble, and that it seemed to depend on what oxide formulation it was.

Ms. Denise Nichols asked if the Capstone researchers had examined eye and oral cavity exposure to depleted uranium and resulting effects. Mr. Alberth stated that there were tear duct models. Dr. Haley noted that there were two different issues: (1) the amount of uptake into the blood system through the eye; and (2) the effects of uptake on the eye and oral cavity. Mr. Alberth stated that the ICRP model had distinguished target organs, predominantly the kidney and bone. He said that there was a lesser dose contribution in other areas. Dr. Steele asked if there were any direct effects or long-term effects on the eyes and oral cavity. Mr. Alberth stated that he would have to defer to a radiobiologist to look at the sensitivity of the cells. LTC Melanson stated that, from a radiation perspective, there were a lot of good data on radiation-induced cataracts. He stated that he wasn't aware of any research looking at the ophthalmologic effects of DU.

Dr. Haley asked if there was any research on the ophthalmologic effects of other heavy metals, e.g., lead. Dr. Briner noted that one had to reach the level for lead encephalopathy before seeing changes in the auditory pathway of the central nervous system. He questioned whether DU would remain in contact

with the eye long enough to have a direct effect, because, for example, it could be washed away by tears. He stated that he would be more concerned about systemic effects.

Chairman Binns thanked the morning speakers.

The meeting adjourned for lunch at 12:05 p.m.

The meeting reconvened at 1:10 p.m.

Gulf War Illnesses and Vaccines: Overview of Epidemiological Findings and Remaining Issues

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

Dr. Steele presented an overview of the epidemiological findings and previous Committee discussions pertaining to GWI and vaccines, along with remaining issues for the Committee to review in this area. (See Appendix – Presentation 12.) While discussing the remaining issues pertaining to squalene antibodies and ill Gulf War veterans, Dr. Steele noted that Drs. Asa and Garry had been invited to present their findings at this meeting. She stated that, unfortunately, they were not able to attend.

Dr. Melling commented that one of the epidemiological difficulties was that the incidence of GWI was pretty much the same among U.S. and U.K. troops, while there were differences among the vaccines these troops received. He noted that some U.S. troops received the anthrax vaccine, while virtually all U.K. troops received the anthrax vaccine. He noted, however, that the British vaccine was different than the vaccine administered to the U.S. troops. He stated that the only commonality, that he could see, was that both vaccines contained protective antigen (PA). He stated that studies were about to begin with purified PA vaccines that would help to address this concern. He noted discussion had occurred about studies that will compare Anthrax Vaccine Adsorbed (AVA) and PA vaccines, and this should be kept in mind. With respect to squalene, he stated that he knew and would swear, as he was responsible for making the U.K. anthrax vaccine, that no squalene was deliberately put into the U.K. vaccine. He acknowledged that this did not rule out the possibility of some squalene contaminant.

Ms. Dykeman stated that it should be considered that, once they were deployed to theater, supplies of vaccine were being received from different, sometimes foreign, suppliers.

20 Studies to Evaluate Adverse Events After Anthrax Immunization

COL John D. Grabenstein, RPh, PhD
Deputy Director, Military Vaccine Agency, U.S. Army Surgeon General's Office
Scientific Director, Biodefense Vaccination Program, Department of Defense

COL Grabenstein gave an overview of research on adverse reactions to anthrax immunization. (See Appendix – Presentation 13.)

Dr. Melling referenced the PA content in the AVA vaccine debate. He stated that he had not seen published data on it, and asked COL Grabenstein if he might have any information to shed light on this issue. COL Grabenstein stated that in January, 2002, the U.S Food and Drug Adminstration (FDA) approved renovations to the vaccine production facility at Lansing, MI. During the process validation, tighter limits on variability between each lot were set, resulting in tighter control. Dr. Steele stated that the GAO report indicated that the change in filters occurred in 1990. COL Grabenstein stated that this

was a separate issue. Dr. Steele asked if there were data as to whether the filter change had caused a change in the mean PA levels. COL Grabenstein stated that he didn't know if these data were kept with the early lots. He stated that the potency test/biological survival index for the vaccine had stayed consistent from 1991-1998.

Dr. Golomb stated that a higher dose of PA wouldn't necessarily be expected to inhibit the potency. She indicated that the GAO report had suggested that there was a 5-100x increase in PA in the vaccine following the 1990 filter change. While lethal factor and edema factor weren't tested for in the U.S. vaccine, these factors were believed to be present in the vaccine in unknown amounts. She stated that there was no way to know whether these were comparably affected, and that there was a presumption that the previous ceramic-based filters caught a lot of anthrax toxin proteins. COL Grabenstein stated that his group was not convinced that the PA assay, which showed an astronomical elevation, was a valid assay. Dr. Melling clarified that GAO had not conducted analytical studies on this matter. He stated that this report quoted unpublished studies conducted by the Army at Fort Detrick.

Dr. Haley stated that the adverse events studied with respect to the anthrax program were not necessarily the outcomes of concern before the Committee. He stated that the Committee was concerned with subtle changes in cognitive function, sensory problems, and other symptoms compatible with GWI. He stated that the outcomes reported were generally self-reported neurological disease, self-reported cardiac disease, hospitalization, etc., which don't correlate with GWI. He stated that he wasn't aware of the CDC clinical trial, and was interested in what outcomes would be measured. COL Grabenstein stated that the SF-36 was one of the instruments being used in the CDC trial. Dr. Haley stated that this was good, and may help resolve unanswered questions. COL Grabenstein also said that there would be comparative immunogenicity studies/antibody studies of the AVA and PA anthrax vaccines.

Dr. Golomb stated that 1/5 of all drugs released to the open market by the FDA are ultimately withdrawn or have major blackbox warnings. Half of reported adverse incidents occur more than 7 years after release to the open market, and adverse effects that lead to these withdrawals normally weren't identified in randomized clinical trials. She said that healthier subjects were typically enrolled in the anthrax vaccine studies, but that one published report had suggested that individuals on medications or having comorbidities have greatly elevated rates of acute adverse effects. She stated that the researchers should actively recruit a population that might be adversely affected to show a complete picture of the vaccine's effect. COL Grabenstein agreed.

Dr. Steele noted that the Sulsky study had found that between individuals who received anthrax vaccine and those who had not, fewer people were seen for disability evaluations among those who received the vaccine. But, when results were stratified by the number of vaccines received, the people who received 1 or 2 doses of vaccine had a significantly higher rate of disability evaluations than those who did not receive AVA. She asked COL Grabenstein for his thoughts on this finding. COL Grabenstein stated that vaccination follows along with selection for overseas travel. He suggested that there was a greater scrutiny of health in individuals deployed overseas. He also noted that there were incubating diseases that weren't clinically apparent at the start of the vaccination series. He stated that the dropout rate between doses of the randomized clinical trial was 1%, and none were attributed to the vaccine, rather, they were attributed to social factors. Dr. Steele asked about the idea that individuals with 1 or 2 anthrax shots may have sought disability evaluations at a higher rate because they had adverse reactions to the vaccine, and so had stopped receiving the doses early in the vaccination program. COL Grabenstein stated that these must not be hospitalization diagnoses, and that he wasn't persuaded.

Mr. Smithson referred to COL Grabenstein's comment that the systemic effects of the anthrax vaccine were similar to other vaccines with adverse reactions affecting 5-35 percent of recipients. (See Slide 8.)

He asked if COL Grabenstein had data to indicate whether these symptoms were considered chronic or not. COL Grabenstein stated that, in this particular case, he was referring to acute effects. From other studies, e.g. Hoptof, these were mostly (99%) short-lived events for the affected individuals. Mr. Smithson asked what education or encouragement to report adverse reactions was being provided to troops at the time of vaccination, in order to avoid the under-reporting errors associated with a passive reporting system. COL Grabenstein replied that there were special tri-fold brochures for anthrax and smallpox vaccines with phone number and website information. He stated that they were trying to get the CDC to do a survey of civilian versus military physicians to determine the level of awareness in these sectors. He was confident that the military physicians would fare well in this survey.

Mr. Robinson asked if any of the studies separated out severe neurological problems. COL Grabenstein stated that the data weren't collected in a format that would support such analysis. He stated that the unusual cases were compiled though the Vaccine Adverse Event Reporting System (VAERS). Mr. Robinson asked if the 1% with serious problems fell under the category of "acute" or whether they were disbursed amongst "fever", "sore arm", and "rash." COL Grabenstein stated that any vaccine could cause side effects. He stated that these reactions could be submitted to VAERS, but that they didn't track down "sore arm" and "redness" reports. He stated that this table was a summary of survey data, and didn't tell the whole story.

Mr. Robinson noted that the Committee was interested in the vaccine used on the first Gulf War veterans. He noted that the Institute of Medicine (IOM) was referring to the post-Gulf War (1998-present) vaccine when it held the vaccine to be safe and effective. COL Grabenstein agreed, and acknowledged the lack of records for the first Gulf War. He stated this makes it difficult to determine correlations between outcomes and exposures. He stated that an interesting issue would be determining the difference(s) between 1991 and 2001-2005 scenarios.

Mr. Robinson asked whether VAERS was still active following the IOM and FDA findings that the anthrax vaccine was safe and effective. COL Grabenstein stated that the VAERS remained in full operation.

Dr. Golomb and COL Grabenstein discussed the statistical findings regarding disability and the anthrax vaccine.

The meeting adjourned for a break at 2:41 p.m.

The meeting reconvened at 2:58 p.m.

Studies on the Health Effects of Multiple Vaccines: Completed and Ongoing

COL Phillip R. Pittman, MD, MPH
Chief, Division of Medicine, USAMRIID

COL Pittman gave an overview of research conducted regarding the health effects of multiple vaccines. (See Appendix – Presentation 14.)

Dr. Melling noted that the Fort Detrick alumni group in the squalene study (Part III) had received their shots over a long period of time. (See Slide 31.) This was different from the high concentration of immunizations given before the first Gulf War. He stated that this study addressed multiple vaccinations, but not multiple vaccinations within a very short period of time. This study was not conducted with GWI in mind, but cast a broad net to analyze a wide range of people. He stated that they could sort the data based upon immunization time intervals.

Dr. Golomb asked if the older alumni in this study, who received the anthrax vaccine before the production changes in 1990, might be distinguished more from those who received the more recent vaccine. She noted that there might have been differences in amount of antigen present in the vaccine, and manufacturing problems might have been more prevalent after the 1990 time period. COL Pittman noted that these differences had been reported. Dr. Golomb commented that the alumni, being a social group, might reflect a healthier subset of individuals who were able to travel and participate in these events. She stated that those with more significant problems might not have been part of this screening pool. She also noted that these were individuals who received an extremely large number of vaccines. She stated that the individuals who might have been vulnerable to problems received fewer immunizations. COL Pittman agreed that many individuals who had reactions found other jobs that didn't require further immunizations.

Dr. Golomb noted that the study had started with 100 more controls than cases, and was curious if this increased the statistical power of the findings and the reason behind doing this, e.g., to match age closer. Mr. Paul Gibbs, statistician on this project, stated that the analysis was stratified to balance these concerns and make the groups more comparable.

Dr. Nass noted that a large proportion of individuals who weren't treated for tularemia would develop chronic symptoms. She asked if antibiotic treatment timing had been considered for the findings relating to these individuals. COL Pittman stated that every individual who contracted tularemia was treated. Dr. Nass stated that she had a Fort Detrick publication that reported that these individuals had the disease for at least a month before receiving treatment. COL Pittman stated that she must have misread the report. Dr. Nass asked whether treatment timelines for those with Q fever had been considered. Dr. Haley stated that he was aware of the studies to which Dr. Nass' was referring, as his group had submitted a proposal a few years ago to replicate them using more modern immunological techniques. He stated that the individuals were treated once symptoms presented.

Dr. Nass noted that COL Pittman had stated that the Fort Detrick alumni squalene study hadn't been conducted with GWI in mind. She noted that the Whitecoat study volunteers, however, had been given a questionnaire that asked about several symptoms relating to GWI. COL Pittman stated the Whitecoat study had been conducted twenty years before the Gulf War, and there was no relationship between the studies. He stated that that there were several symptoms investigated, but they were not limited to GWI type symptoms.

Dr. Haley noted that earlier studies, e.g., Peeler, were flawed with the potential for the healthy worker effect. He stated that these studies were so flawed and uninterpretable that they detract from the

argument, unless heavy caveats are provided. He noted that more definitive evidence and better analyses, hopefully, would be coming from future studies, e.g. the CDC clinical trial. Dr. Golomb noted that, despite the caveats, the last study by COL Pittman's group was well done.

Mr. Robinson asked if the DoD vaccination records for the current conflict were better than for the first Gulf War, providing information about the exact date and schedule at which immunizations were given. He asked if COL Pittman would be examining multiple vaccinations given in a short period of time. He stated that some military personnel refer to these as "gang vaccinations." COL Pittman stated that the data hadn't been previously analyzed this way, but they would consider doing it.

Vaccinations and Illness in Persian Gulf War Veterans

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

Dr. Golomb discussed various issues involving vaccines, with an emphasis on the anthrax vaccine, including their efficacy, safety, manufacturing, chronic effects, administration of multiple vaccines, adjuvants and cytokines in relation to immune modulation, and the controversies surrounding all of these issues.

Upon conclusion of her talk, Dr. Melling commented that, in his opinion, the issue wasn't that the vaccine was ineffective. Because Phase 3 studies cannot be done, he stated that a number couldn't be placed on its efficacy. He stated this was a problem. Dr. Golomb agreed that this was a fair statement.

Dr. Meggs asked about the symptoms evidenced in the various animal models and whether they were representative of human symptoms. Dr. Golomb stated that while there may be similarities between the disease manifestations of various species, the real issue was whether there were similar reactions to vaccine. She indicated that there was evidence that suggested that human responses do differ from those of test animals. She noted that a single inoculation was enough for most animals, but that was not the case for humans. Dr. Nass stated that rhesus monkeys, which weigh 10 pounds, were given a human dose of anthrax vaccine. Dr. Golomb noted that many of the studies with rhesus monkeys had no control animals, so it is unknown whether the rate of survival is higher in vaccinated animals. She did reference one published controlled vaccine study. She stated that they found nine out of ten anthrax-vaccinated monkeys survived, but that nine out of ten control monkeys survived, too. COL Grabenstein noted that this involved post-exposure prophylaxis versus pre-exposure protection, and that the controls were not part of the 65 vaccinated monkeys. Dr. Golomb stated that her point was related to study design, and that unless there was a control group for the study, it was not clear what inferences to draw. She stated that she wasn't saying that the anthrax vaccine didn't confer protection, but that the quality of the published evidence was weak. Dr. Nass stated that there was an unpublished study in which vaccinated monkeys became sick after exposure to anthrax, but eventually survived.

Mr. Robinson asked when the RAND report on vaccines, which Dr. Golomb had authored, would be released. Dr. Golomb stated that she didn't have an exact date, but believed it would be soon. She stated that there had been scheduling issues for both RAND and her. She stated, however, that she didn't believe there was malintent by either party in the delay of the report's release.

Dr. Haley asked what Dr. Golomb would recommend be done next with respect to anthrax research. He stated that the troops needed to be protected from an anthrax attack, and hoped that the right studies had been performed to do this. Dr. Golomb stated that a large-scale, randomized trial, which used health outcomes relevant to Gulf War veterans, was needed. She noted that care was needed to not exclude the

subgroups that potentially would be the most susceptible to the vaccine's effects. She also noted that even if the current anthrax vaccine was found to be safe, this wouldn't necessarily have implications for the relationship of anthrax vaccine and health problems in Gulf War veterans. However, if there are problems, such as with production methods, she stated it would be reasonable to infer a relationship between anthrax vaccine and illness in Gulf War veterans.

General discussion occurred about the recent litigation involving DoD's anthrax vaccination program.

Chairman Binns asked Dr. Golomb if there was anything more or different that should be done, in light of the CDC's clinical anthrax trial. COL Grabenstein stated that the CDC's study was a placebo control, randomized, multi-center, double-blind trial. He said that they were looking at a stable population, with no healthy warrior effect, over a long period of time (25 years/person). He stated that there were approximately 1600 participants, with 1/6 receiving a placebo and the other 5/6 receiving various dosing regimens. Mr. Robinson asked if there were any concurrent studies at Walter Reed in which military subjects were vaccinated and then had blood drawn immediately afterward. COL Grabenstein replied that Walter Reed was one of the five sites that enrolled civilians, but not military personnel. He stated that Walter Reed hospital may draw blood for clinical use in military patients who received the anthrax vaccine, but there were no studies to draw blood for banking.

Chairman Binns thanked Dr. Golomb, and opened the floor to discussion.

Dr. Steele asked COL Grabenstein if there had been any discussion about or actual studies of squalene antibodies in ill Gulf War veterans. COL Grabenstein stated that he thought Dr. Alving was planning on analyzing blood samples of Gulf War veterans, but he didn't know any specifics about the study.

Mr. Robinson asked COL Grabenstein if he had oversight of or worked for the vaccine injury clinic. COL Grabenstein stated that there was a Vaccine Health Care Center with four sites. He stated that he did not have oversight of the Vaccine Health Care Center. He stated that he was at the Army Surgeon General's office. Mr. Robinson asked if the Committee could get information from the Vaccine Health Care Center with respect to: (1) the numbers of personnel seen, (2) what illnesses were being claimed, (3) disability outcomes, and (4) the number of those compensated for vaccine-related injury. COL Grabenstein stated there were patient records, and if provided with a list of questions, he believed the Vaccine Health Care Center would try to provide answers.

Dr. Steele noted that epidemiological studies of Gulf War veterans consistently showed some relationship between increased illnesses and vaccines. She also noted that the long term follow-up studies of anthrax and multiple vaccines presented today hadn't evidenced a similar problem. She asked the group for their thoughts on how to reconcile these findings. Dr. Melling stated that, at the time of the first Gulf War, the troops were subject to many "insults." He asked how epidemiologists had been able to tease out what vaccine was the problem. Dr. Steele stated that she did not know of any epidemiological studies that had looked at interactions between other types of exposures and vaccines. However, researchers had controlled for multiple exposures and found risk factors that weren't related to vaccines and risk factors related to vaccines.

Dr. Haley stated that his review of the epidemiological studies had revealed two types of studies, i.e., those that looked at organophosphates and those that didn't. He stated that those that focused on organophosphates didn't show any immunization effects, while those that didn't showed immunization effects. The ultimate study would measure all of the risk factors, and then control for the strongest risk factors. He stated that, in his view, immunization as a risk factor would not stand up. He believed there were confounding effects with other risks, e.g., going into combat, likelihood of taking pyridostigmine

bromide, being exposed to pesticides, etc. Dr. Steele stated that there had been subgroup analyses in some of these studies. In groups stationed in areas with multiple exposures, the odds ratios of people getting vaccines wouldn't show up as important because the people getting sick have other exposures that may look more important. Dr. Haley stated that this might be an issue that needed to be teased out through the Committee's literature review. Dr. Steele stated that the Committee staff would be presenting this type of summary review at a future meeting, but that there weren't published studies that examined the issue in this way.

Dr. Golomb stated that there would be measurement error in each variable, and that measurement error would be associated with outcomes. Dr. Melling stated that the overlap between those who received vaccines and those who took pyridostigmine bromide must be huge. Dr. Golomb stated that she didn't believe that anthrax vaccine was the "smoking gun" with respect to Gulf War illness, but this did not mean that it couldn't be contributing to the risk and effects in ill veterans. She noted that the Unwin study did include organophosphate and vaccine variables, and found effects for both. However, the strongest risk ratios were with the organophosphate exposures. There were more people exposed to pyridostigmine bromide, which had a stronger risk ratio. Thus, the attributed risk was likely to be greater for the organophosphate exposure, meaning more individuals' illness is likely to be attributable to this exposure. Dr. Haley stated that this is where the Committee needed to go in the next report, looking at these issues very carefully.

Dr. Meggs asked, given the number of Gulf War veterans who have become ill, if the anthrax vaccine or multiple vaccines were the sole cause, wouldn't more veterans have problems. Dr. Nass stated it might depend on doses.

Ms. Dyckman stated that the problem is that DoD was the one doing the studies, and nobody trusted its findings. She noted that when a solider enters the military, he or she is forced to be vaccinated. She stated that, if an individual has a problem at the Naval Academy with a vaccine, they weren't commissioned and so are not seen in the data pool. She said there needed to be another study from a credible source. She wasn't opposed to vaccines, but wanted information about potential adverse effects. She stated that these studies were very political, and was hesitant about trusting CDC involvement in this research too.

Chairman Binns asked whether there was any reason to think there were causal factor differences, with respect to GWI, between U.S. troops and U.K. troops. Dr. Haley stated that some brainstorming was needed with regard to Dr. Hoptof's data on pre- and post-deployment vaccination. He stated that it should be examined in more detail. Discussion occurred about the findings of both Dr. Cherry's and Dr. Hoptof's studies.

Dr. Melling noted that it was important to look at the differences in the vaccinations received by the U.S. and U.K. troops. He stated that virtually all U.K. forces received one or two anthrax vaccines, while no more than 1/3 of the U.S. troops did. He stated many U.K. forces received plague vaccine, but didn't believe that U.S. troops had received this vaccine. He noted that the situation was reverse for the botulinum vaccine. He stated that, considering this, the vaccine link looked weak. He noted that both U.S. and U.K. troops were taking pyridostigmine bromide, spraying tents with organophosphate pesticides, and present when chemical alarms were sounding. Dr. Steele noted that there were ill individuals who hadn't been exposed to these other factors. Ms. Dyckman stated that the U.S. and U.K. medical forces worked together and exchanged patients. She stated that some vaccines were "brought in", while others were bought on the open market.

Dr. Golomb commented that she thought the strongest causal evidence for the most ill veterans related to chemical exposures and cholinesterase inhibitors. She stated that this was not necessarily exclusive though, and individuals may be ill for different reasons. She stated that it was important, with the current anthrax vaccine, to determine the long-term safety profile of the vaccine.

Chairman Binns asked for the veterans' thoughts on the issue of vaccines. Mr. Robinson said that the issue wouldn't be on the table if there hadn't been stonewalling in admitting that there was a problem. He stated that it was also an issue for those individuals who were injured and had been left without recognition or compensation. If veterans had been advised of the adverse effects, and were taken care of when these effects occurred, there wouldn't be a need for this discussion. He stated that veterans recognize that there are many emerging threats, and that there is a need for the best protection available. He said that he didn't work with individuals who were anti-vaccine, but that they were anti-bad-vaccine. It hurts the discussion when even the most small and minute effects won't be acknowledged. Even after the IOM report, new generation vaccine research would proceed. He stated that this might solve the problem, but it didn't answer the questions about 1990-1991 Gulf War veterans. It was important that the problems from the first Gulf War not be repeated with a new generation of soldiers.

Mr. Robinson stated that the U.S. Department of Health and Human Services (HHS) had asked for authorization to start using the vaccine due to an unknown, unspecified threat. It was not just a protection issue, but was also a political issue, and that there was a move to subvert the federal court action. He asked for open honesty from the government. He asked COL Grabenstein if he knew what the potential threat was that prompted the HHS actions. He asked what had changed, in terms of threat, from the time DoD was able to give the anthrax vaccine mandatorily and now. COL Grabenstein stated that the threat relates to the fact that anthrax is deadly and it doesn't require an elaborate delivery system. He stated that it was an emergency because there were adversaries out there who could use weapons against us. He indicated that there was no need for an FDA emergency use authorization to enable this vaccination program until the federal court's ruling. Therefore, there were troops vulnerable to enemy weapons now. Mr. Robinson asked if the emergency use authorization was going to be localized to a region and threat-specific area, or offered to the entire armed forces. COL Grabenstein stated that it would focus principally on Central Command and Korea.

Mr. Smithson stated that there was a major distrust factor when it came to the anthrax vaccine. He stated that this was a reality that must be addressed. He stated that there were, among the Gulf War community, different camps that were convinced that one particular exposure caused their problems. He stated that the research needed to explore all areas, but needed to focus on multiple exposures. He stated that he didn't believe one particular thing caused the reported problems. He stated that good research was needed, but always keeping in mind people's perception of this research.

Public Comment – Day 2

Chairman Binns opened the floor to public comment.

Ms. Val-Hammack spoke to the Committee. She stated that communication and information were stumbling blocks. She said that the Persian Gulf War Registry, the Gulf War Health Review, and physician continuing education about Gulf War concerns had disappeared. She had visited VA medical centers that have no information for Gulf War veterans in their lobby, and has approached patient advocates in VA facilities who didn't know about Persian Gulf surveys. She stated that the veterans were not being advised of the changes and whom to contact for help. She expressed her shock at the low numbers of veterans being seen at the War-Related Illness and Injury Study Centers (WRIISCs). She

stated that the veterans were not sure that the Committee had access to reasonable evidence, specifically the survey data and clinical practice guidelines follow-up. She said that the Gulf War Veterans Information System (GWVIS) report provided only an executive summary, not a breakdown of the data. She suggested that the Committee's charter should be modified so that it could review treatment protocols. Veterans see VA's Office of Research and Development (ORD) as a stumbling block for the Committee, and it didn't appear that ORD had responded to the Committee's 2004 report findings and recommendations. She stated that the announced additional research funds appeared to be an illusion. Chairman Binns stated that this issue would be addressed the following morning.

Ms. Dykman spoke to the Committee. She stated that health data were collected at the fleet hospital to which she was assigned. She stated professionals staffed this pre-positioned hospital, some of whom planned to conduct studies from this data. She stated that inquires needed to be made to find out what happened to these records.

Dr. Nass thanked Drs. Golomb and Steele for their superb compilation of information regarding the issues pertaining to vaccines. She stated that she had six points that she wanted to make:

(1) The Cochrane Review had changed. Tom Jefferson, who was the main author on the first study, had stated there was no evidence for the anthrax vaccine's efficacy.
(2) There were studies in 1967 and 1968 conducted at Fort Detrick, regarding protective antigen's intrinsic toxicity that had not been followed-up in the public literature. She stated that she believed that protective antigen had intrinsic toxicity, but that the information currently available was only suggestive and more meaningful toxicity research was needed. Dr. Melling asked if Dr. Nass could provide him with these references, and she indicated she would.
(3) The IOM report used a different method for drawing their conclusions, but didn't identify what method they did use, specifically, what weight was given to what studies.
(4) CDC had received millions of dollars from DoD to conduct their anthrax studies. She noted that an initial *Morbidity and Mortality Weekly Report* (MMWR) article had cited two earlier (mid-1990s) CDC studies showing that anthrax vaccine was unrelated to Gulf War illnesses, but that neither of the studies cited had the ability to make that determination. She stated her belief that CDC was somewhat suspect. She was looking forward to reading the CDC's clinical anthrax vaccine trial findings, but was cautious about them.
(5) There had been a couple hundred submissions to the FDA anthrax vaccine docket. She recommended that the Committee request access to these submissions to get a feel for what other people were saying about the anthrax vaccine.
(6) There was a need for independent researchers to conduct the studies in this area. She stated her belief that it was impossible to get an independent, prospective study through DoD. She stated that the next best thing would be a retrospective study of veterans who have/have not received the anthrax vaccine.

Ms. Nichols spoke to the Committee. She said that there were veterans who were afraid to come before the Committee, and that they needed to have more than five minutes to address the Committee. She stated that there was a need to facilitate information exchange between the Committee and the veterans. She stated that the VA and DoD needed to help find the doctors who had information. She asked for an executive summary of the Committee's meetings. She had spoken with several Congressmen who weren't aware of the Committee and its report. She asked that the GWVIS report show what ratings were being assigned to Gulf War veterans with undiagnosed illnesses. Mr. Smithson stated that the report delineates those as "10% or more" and "0%." Ms. Nichols stated that was a wide range, and should be broken down further. She stated that the studies needed to be open recruitment, and more effort was needed to bring in Gulf War veterans for these studies. She expressed her appreciation for what the

Committee was doing, and thanked the Committee for allowing some participation from the audience in this meeting. She addressed the DoD officials in the room, and stated that veterans were not the enemy. She stated that it was time for atonement and to move things along, considering the new conflict.

Chairman Binns thanked the meeting's participants for being there. He thanked COL Grabenstein and COL Pittman for presenting, and noted that they were there on "active duty." He thanked the veterans and members of the public who had traveled to contribute to the day's conversation.

The meeting adjourned for the day at 5:35 p.m.

The meeting reconvened Friday, April 8, 2005, at 8:35 a.m.

Report to Research Advisory Committee on Gulf War Veterans Illnesses – April 2005

Brian G. Schuster, MD, FACP
Director, Clinical Science Research and Development Service
U.S. Department of Veterans Affairs

Chairman Binns introduced Dr. Schuster.

Dr. Schuster gave an overview of activities and progress in VA's Gulf War Illnesses research program since the last Committee meeting. (See Appendix – Presentation 15.)

Dr. Meggs asked whether a Committee representative could be present at the April 20, 2005, treatment center meeting. Dr. Schuster stated that Dr. Steele would be attending the meeting. He said that it would also be a good idea to get together more frequently to discuss and identify other high priority issues, and develop more specific research funding announcements (RFA).

Mr. Graves inquired about Dr. Schuster's comment concerning lung cancer and oil well fires. Dr. Schuster stated that there might be an association between exposure to the smoke of the fires and lung cancer. As such, he stated that lung cancer research could become part of research efforts related to toxic exposures, and then would fall under deployment health research.

Dr. Steele asked Dr. Schuster about VA's ability to create focused RFAs. She stated that this seemed to be a common sense approach, but had understood this was difficult to do at VA. Dr. Schuster stated that deployment health research had tried to take this approach, i.e., identify key questions for Gulf War I illnesses, and then try to focus on these issues. He stated that the approach that had been taken was more like a "shotgun" approach, which diluted the program. Dr. Steele stated that the Committee had understood that the funding announcements had to be kept broad, and was pleased to hear that more specific and focused RFAs were possible. Chairman Binns stated that he was delighted to hear this too. He noted that the Committee's 2004 report contained over 50 recommendations, and it wasn't feasible to fund all of them. He stated it was good to know that the focus could be placed on a few high priority areas, and making them part of a plan. Dr. Haley stated that he was delighted to hear this news too. He thought it would be useful to explore extra mural funding coordination with the National Institutes of Health (NIH), FDA or DoD. In 1998, Congress gave the Secretary of the Department of Veterans Affairs oversight of the whole investigation into Gulf War-related illnesses. He stated that back in the early 1990s, at the start of the Clinton administration, there was a decision made that NIH and CDC were to stay out of this area of research. The decision was made that DoD and VA would be the primary agencies conducting this research. He stated that this hampered involvement by the private and university research communities. Dr. Schuster noted that research dollars had been in decline for all agencies, including VA.

He stated that, in the last six to eight months, there was a real willingness for the agencies to work together to leverage the research monies that were available. Dr. Haley stated that his group had been working with DoD over the past couple of years, and noted they were increasingly willing to solve these problems. He stated that VA was working with DoD on current deployment issues, and there was a precedent for more collaborative work between the two agencies. He thought that, in the past year, there did appear to be a positive change taking place within DoD and VA, but that NIH needed to be sent the message that it was okay for them to fund research for Gulf War veterans. Dr. Schuster stated it all depended on how the research solicitation was developed, and how both agencies' interests were addressed. Dr. Meggs commented that there was an NIH policy that if a proposal mentioned "Gulf War", it was not considered for NIH funding and applicants were directed to VA. He stated that one of the Committee's first recommendations was to open up this issue to a broader range of researchers, and that this required different agencies' help. A general discussion occurred about the source of VA research dollars and how these monies are awarded to researchers, inside and outside the VA.

Discussion turned to the proposed VA treatment center. Dr. Schuster stated that discussions were underway as to the center's organization. He stated that he was leaning towards creating a virtual center of expertise, while others might believe it should be a grounded, physical location. Based upon his experience, the affected patients were likely to be all over the country, and that creating a geographically-centered location might be more limiting compared to a virtual center. Dr. Meggs stated that, in conversations with the Durham VA, he found other researchers who were not sure how to identify these veterans.

Dr. Schuster discussed the VA's Vietnam twin registry. Dr. Meggs asked if a non-VA researcher could apply for NIH money to study twins through this registry. Dr. Schuster stated that it was done. Dr. Meggs said that, in the case of Gulf War illness, the proposal wouldn't be considered. Dr. Schuster stated that most of the non-VA investigators were not using the Vietnam twin registry to study distinctions between deployed and non-deployed twins. They were studying non-veteran health issues for which a twin pair would help answer the question.

Dr. Golomb asked for clarification of the proposed mechanism for joint VA/NIH proposals for Gulf War illnesses. Dr. Schuster stated that there had been several proposals like this, which had been organized in different ways, e.g., NIH paid for the non-VA patients and non-VA sites and VA paid for the VA patients and sites in a multi-center trial. He stated that VA money must be spent on VA investigators and VA sites. Chairman Binns noted that VA did not have a mechanism to routinely fund non-VA investigators, and that he was pleased to hear about other options to generate outside research in this area.

Chairman Binns asked that the Committee return to its discussion about the proposed treatment center. He stated that Dr. Steele would be representing the Committee, but asked the individual Committee members to provide their ideas of what should be brought to the table. Dr. Steele stated that it should be clarified that this center was not being designed as a clinical treatment center for veterans, but rather a research center for treatments. She stated that a multi-site center wouldn't necessarily mean more veterans would be treated in more locations. Dr. Schuster clarified that his earlier comments had been directed at the need of having a veteran population available for study.

Chairman Binns asked for the Committee's thoughts about having a single physical site, with several researchers located together, versus a multi-site virtual treatment research center, where collaborating researchers are all over the country.

Dr. Golomb stated her preference for the multi-site, virtual center, because it avoids dominant, restrictive approaches that might drive the entire group's work at a single site.

Dr. Haley stated that there were several tough problems to getting productive outcomes from a treatment center like this. He stated that the first one was classifying Gulf War veterans, and there was a need to designate these veterans into homogenous "bins." He stated that it would be exciting if this was accomplished. Dr. Schuster stated that the working group needed to look at the state-of-the-art on that particular issue, identify the questions that should be addressed, and find the means to implement these ideas into studies. He stated that, in the VA's cooperative studies program, they implement very large trials in 20-40 centers that may last several years. He stated that VA had mechanisms and expertise to plan these studies very carefully. He stated, though, that many of the Gulf War illnesses patients are probably not in the VA system.

Dr. Meggs provided a counter-argument based upon his experience with MCS. He stated that a localized facility would help facilitate people through the study process. Dr. Meggs stated that a multi-center trial was ideal for many situations, e.g., drug studies. Dr. Schuster stated that the job of the center's working group would be to decide if an issue was important to study and develop the study plan. He stated that it was important to have a knowledgeable group that comes together to identify and test hypotheses.

Ms. Knox stated that it was very important to have the center spread across the country so more veterans would have access. Even though she was a Gulf War veteran, she didn't utilize the VA medical system because of the long waits. It was important to capture other veterans who do utilize the VA system for healthcare. She also stated that it was important to look at where the Gulf War population was located. A majority of these veterans are in the southern United States, but most of the VA medical centers were in the northeast United States. She stated that this raised the issue of using non-VA facilities in this type of research.

Dr. Steele asked Dr. Schuster whether non-VA clinicians could be involved in developing the virtual center. Dr. Schuster stated that they would be able to be involved so long as no VA appropriated dollars were paying for their participation.

Mr. Robinson stated that Gulf War veterans are consistently being approached by "snake oil salesmen" with potential cures. Occasionally, there is someone, not within the VA or DoD, who is treating the veterans with beneficial results. Dr. Schuster stated that this would be the role of the working group, investigating the state-of-the-art ideas available and develop them further. Chairman Binns concurred that the purpose of the center was to institutionalize this approach.

Mr. Graves asked whether it was possible to have Gulf War coordinators at VA medical centers. Mr. Smithson stated that these coordinators do exist. He noted Ms. Val-Hammack's comments from the previous day about the inability of veterans to locate them. He stated that he had faced similar problems in VAs around the country. He stated that the Committee needed to reenergize the emphasis on these coordinators, as well as updating the VHI series on Gulf War illnesses.

Chairman Binns noted that the discussion was leaving the research track, but acknowledged that it was an important issue relating to the practical aspects of VA health care for Gulf War veterans. He stated that he would allow discussion with Dr. Schuster on this topic, but asked that it be kept brief.

Ms. Nichols stated that signs needed to be place in VA medical centers, directing veterans to the Gulf War coordinators. She asked Dr. Schuster if the VA's Vietnam twin registry could also be utilized for Gulf War veterans. Dr. Schuster stated it could be done, but it would be complicated and would have to be funded. Ms. Nichols stated that, if a biomarker study was being considered for Gulf War illnesses, a twin registry might be beneficial in this research. Dr. Schuster stated that the working group would have

to look at the best way to study biomarkers, noting that there were other methods that might be more cost effective.

Ms. Val-Hammack asked for clarification about the separation of ORD and the Deployment Health Working Group. Dr. Schuster stated that ORD was tasked with writing up the results of the working group, and that VA had a seat on this committee. He noted that a temporary VA appointment was in place, but said that once a new ORD Gulf War coordinator was hired, he or she would be assigned to this position.

Chairman Binns stated it was good that Dr. Schuster, while focused on research concerns, could hear the veterans frustrations related to the local medical centers. Dr. Schuster stated that this actually was one of ORD's four research areas, i.e., Health Services Research and Development (HSRD). Mr. Robinson asked who the contact person for HSRD was. Dr. Schuster stated that this was Dr. Shirley Meehan.

Chairman Binns thanked the Committee for its input on the upcoming treatment center meeting. He stated that individuals scheduled to participate included: Dr Steele, Dr. John Concato, Dr. Roberta White and Dr. Wayne Jonas. Dr. Steele provided the Committee with background information about Dr. Jonas.

Chairman Binns asked Dr. Schuster about the expected funding of the FY05 RFA. He stated that the Committee had understood that former Secretary Principi had committed up to $15 million for new research. He noted that previously-funded studies, some of which were classified as brain and nervous system research, were really post traumatic stress disorder (PTSD) research. Dr. Schuster noted that not all of the studies listed in his presentation were focused on PTSD. Chairman Binns acknowledged this, but stated his wish to see a higher number of non-PTSD studies funded with the new RFA. Dr. Schuster stated that the $3 million figure was simply a projected amount, based upon past RFA performances. He said that more funds might be allocated if more study proposals were received. Chairman Binns thanked Dr. Schuster for the clarification.

Ms. Knox noted an earlier meeting presentation by Dr. Clauw, in which he discussed his group's development of an internet-based CBT training program. She stated that this approach might be a way to reach more veterans. Dr. Schuster stated that there was a VA web-based PTSD treatment, developed in Canada, which might be applicable to other areas. He stated this form of treatment was evolving, and agreed it might be beneficial for Gulf War veterans.

Mr. Robinson asked whether the Committee/Committee staff was aware of the specifics of the currently committed funds ($9 million) for Gulf War studies. Dr. Schuster stated that he had shortened his presentation due to Secretary Nicholson's scheduled visit, but would be more than happy to provide more detailed information about these studies. Dr. Steele asked for clarification of the FY05 and FY06 allocations. Dr. Schuster noted that FY05 funding was for two years. He stated that ORD's current commitment was for $9 million. He stated, with the additional studies and the carryover from FY05, approximately $15.3 million would be spent in FY06. He stated that more discussion was needed to keep the focus on the high priority issues, which included Gulf War I concerns.

Dr. Steele asked Dr. Schuster to comment on the research enhancement award program (REAP) funding. She stated that there was a 2004 REAP announcement, inviting proposals relating to deployment health and Gulf War veterans' illnesses. Dr. Schuster stated that, due to decreases in FY05 funding, only five to six new programs were started this year. He stated that there were REAPs that dealt with environmental and toxicology issues.

Chairman Binns inquired as to how quickly high-priority RFAs could be developed and announced. Dr. Schuster stated a working group needed to be established, which could even write the RFAs themselves with ORD headquarters approval/oversight. Chairman Binns stated that he was glad to hear this.

Dr. Golomb asked if there might be a mechanism where outside researchers could apply for VA funding with the condition that, if the funding is granted, they will commit 5/8th of their time to VA. Dr. Schuster said that this was possible, and had been done.

Chairman Binns opened the floor to audience questions, and asked them to limit their comments to questions as the Committee was experimenting with audience participation in the discussions.

Mr. Albert Donnay, an audience member, noted that many veterans with undiagnosed illness had left the VA system because the VA had nothing to offer them in terms of treatment or benefits. He stated that these veterans needed to be encouraged back into the system. Dr. Schuster stated this is an approach that the VA would initiate as its research program found more answers. Mr. Donnay stated that guidance or training for physicians inside and outside the VA on Gulf War research was needed. Dr. Schuster stated this was part of the purpose of this project, e.g., take things that look like they need to be validated, and do the research.

Ms. Nichols stated that it had been a while since there had been a VA sponsored Gulf War symposium. Chairman Binns stated that he believed more was being done now in small meetings. Ms. Nichols stated it should be considered for the future to invigorate the process at a local level. Chairman Binns stated that there was a need to have workable options to present at such a meeting. It would be a disservice to "sound the alarm", invite the veterans to come into the medical centers, and not have armed the physicians with diagnostic tools or treatments.

Mr. Robinson agreed that many Gulf War veterans weren't in the VA system because the physicians didn't know how to treat their symptoms. He stated that the veteran service organizations were working to bring veterans back to the system, providing them with information and support.

Chairman Binns noted that the development of a Gulf War veteran brain bank was a much-discussed project. He stated that he had come to appreciate the project's importance through Dr. Paul Greengard's comment that "a lot could be done with one good brain." He asked Dr. Schuster for his thoughts about the possibility of getting this done. Dr. Haley stated that he believed a Temple University/VA researcher had proposed a cooperative brain bank for Vietnam/Gulf War veterans. Dr. Schuster stated that, as the director of the Cooperative Studies program, he had not seen such a proposal. He stated that, if it had a strong rationale or priority, it would be considered.

Ms. Knox stated that Dr. Schuster's comments were "a breath of fresh air."

Chairman Binns thanked Dr. Schuster. Dr. Schuster announced that there would be a presentation later that morning by a stress researcher looking at the current deployment. Chairman Binns acknowledged that the Committee was aware of the importance of stress studies to the current war.

The meeting adjourned for a break at 9:55 a.m.

The meeting convened at 10:15 a.m.

Update on Research in Persian Gulf Veterans – April 2005

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

Dr. Golomb provided an overview of recent research findings relating to Gulf War veterans' illnesses. (See Appendix – Presentation 16)

Discussion followed regarding the cited studies' controls for measured illnesses and deployment/non-deployment. Dr. Haley stated that a weakness in this literature is the use of exploratory factor analysis in the deployed and non-deployed groups, concluding that if they produce similar-looking factor analyses, this means they have the same structure. He stated that what needed to be done was the development of a factor model in one group, followed by structural equation modeling to describe that model in a series of equations, to then determine if the model fits rigorous testing criteria. Dr. Golomb and Dr. Steele stated that this approach shouldn't be used for a case definition. Dr. Haley stated that if there was a unique syndrome, it should come out of the different factors. He stated that developing two exploratory factor analyses that can be made to look the same wasn't necessarily relevant to whether the symptom structure is present in the groups.

Ms. Knox asked if there was a way to document weaknesses of the scientific approaches in this type of study, so that non-experts are aware of these problems. Dr. Steele stated that letters to the editor were one option. Dr. Golomb mentioned that a colleague had proposed a comment section on Medline. Dr. Haley stated review articles are also a way to point out these problems.

Ms. Nichols asked if there was possibility of creating a forum on the Committee's website. Dr. Haley stated that commentary on articles was a subjective matter, and the debate can become contentious and self-serving. He stated that the most productive approach was to focus on a carefully prepared report that focused on the big issues and potential advances in this field. Dr. Steele noted that, when speaking from the Committee's website, the message should be a consensus, not individual opinion.

Chairman Binns thanked Dr. Golomb.

Chairman Binns stated that Dr. Schuster had provided a good overview of ORD's activities. He said that the Gulf War illness study RFA had just been announced, and copies were provided in the Committee's notebook. He pointed out that there was a direct relationship between the amount of good research that would come from the RFA and the number of valid submitted proposals. He encouraged the scientists present to encourage their colleagues to work with VA in submitting proposals under this RFA. He noted that treatment development was receiving the highest priority.

Chairman Binns stated that ORD had announced the formation of a merit review board dedicated to Gulf War research. He stated that the Committee had submitted the names of 53 potential and qualified candidates for this board. He stated that hiring announcements had been sent out for a Gulf War research portfolio manager. He stated that the Committee was not involved in this process, but may ask ORD for a chance to provide input on the candidates. He noted that Dr. Steele had spent a considerable amount of time assisting ORD in developing the RFA. He stated that he would love to see the Committee be able to step back and become advisors once again. He noted again that it was positive and refreshing to hear Dr. Schuster's views on this issue.

Chairman Binns noted that a new Chief Research and Development Officer (CRADO) would be appointed soon. He stated that this person's outlook on Gulf War illnesses would be important. He also indicated that Dr. Jonathan Perlin had been confirmed as VA's Undersecretary of Health. He stated that it

was a positive step to see an individual with some background in Gulf War illnesses, i.e., a former acting CRADO, in this position.

Chairman Binns stated that he had spoken with Secretary Nicholson, and Secretary Nicholson had recognized the importance of Gulf War illnesses. Secretary Nicholson had expected to meet with the Committee for a full briefing and discussion. He stated that the Committee understood that Secretary Nicholson's schedule had been changed to allow him to join the U.S. delegation attending Pope John Paul II's funeral.

Chairman Binns stated that the outcome of the treatment development center meeting would be a key thing to observe in the coming months. He noted the importance of involving other agencies in Gulf War illnesses research. He pointed out that Congress had appropriated an additional $5 million for Gulf War illnesses research by the DoD. These monies had not been committed, but the portfolio managers had done an excellent job of soliciting input from the Committee and the Congressional members/staff who were involved in securing the appropriation. He believed this DoD investment would be well spent. He noted the Committee's recommendation that Congress spend $30 million for the next several years on Gulf War illnesses research.

Chairman Binns thanked the Committee's staff for their hard work. He noted that all of the Committee's documents, including all of the meeting minutes, were available on the Committee's website. He thanked Dr. Meggs and Dr. Golomb for presenting at this meeting. He thanked Dr. Steele for sharing her expertise and putting together the entire meeting.

Chairman Binns stated that former Secretary Principi had deferred Committee appointments and reappointments to incoming Secretary Nicholson. He didn't interpret the lack of action as a signal either way as to the Secretary's position, as the Secretary's slate was full, and this was just one of many items that needed to be addressed.

RAC Committee Business

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

Dr. Steele provided the Committee with an overview of Committee activities, including plans for upcoming meetings and reports. (See Appendix – Presentation 17.)

Dr. Steele asked Committee members if there were additional exposures that the Committee should investigate. Dr. Golomb stated that she saw fuel, paint, and solvents combined into one category, and an important area to consider. Dr. Melling noted the previous day's discussion of risk factors in relation to vaccines and organophosphates. He stated that there would be merit in doing further epidemiological evaluation. Dr. Steele agreed, and stated that this would fall into the presentation's second and third bullets, i.e. pull together and analyze the information about risk factors and not just list them. Mr. Graves stated that the Committee shouldn't look at any of the listed exposures, because they were all toxic. He stated that, in the wider scope of the Committee's mission, he didn't think these additional exposures played a major role for the majority of ill veterans. He stated his belief that the Committee should try to nail down the major potential causes, e.g. depleted uranium, organophosphates, etc., first. Dr. Steele stated that it might be a combination of different things that made an individual Gulf War veteran ill. Dr. Meggs stated that the Committee should be comprehensive, while mindful of the weight of the evidence for each exposure. Mr. Robinson stated his belief that the Committee would be widely criticized if it

didn't examine all known exposures. He stated if a particular exposure showed a higher likelihood of being a problem, it should receive greater attention.

Dr. Golomb stated that, if larger categories, e.g., solvents/heater exhaust, were examined, it might involve more veterans. Dr. Steele stated that there could be an "other" category which addressed the less prominent exposures. She asked for ideas about what should be included in this "other" category. Dr. Golomb stated that this would be defined by the literature. Mr. Robinson stated that the Committee might look at the environmental factors present as a result of the industrial complexes or bombing in the area. He stated he wasn't sure if relevant data existed, but noted that soldiers were being housed near these complexes. He noted that environmental monitoring was now being done, and could be reviewed. He gave an example of soldiers being stationed near a lead smelting factory in Bosnia, resulting in them having high blood lead levels. He suggested that USACHPPM might be able to provide information on this matter.

Dr. Golomb stated, with respect to the Committee's review of methodological issues, that the Committee might comment on researchers being clear on what methods were used, but should not set forth research guidelines. Dr. Steele noted that more progress had been made in CFS and FM research because standards had been established. Dr. Haley stated that he agreed with Dr. Golomb. He stated that the Committee shouldn't be too prescriptive, but should try to bring some order out of chaos. Mr. Robinson suggested a "best practices" approach. Dr. Steele noted that, while the case definitions for CFS and FM were developed for research purposes, it had resulted in patients being able to be diagnosed clinically.

Mr. Robinson stated that the Committee's 2006 report should be presented before Congress in a formal hearing.

Ms. Nichols suggested that the Committee review electromagnetic fields as a possible exposure of concern. Ms. Knox asked for clarification about the electromagnetic fields. Mr. Robinson stated that, when he worked at DoD's Office of the Special Assistant on Gulf War Illnesses (OSAGWI), he had compiled information on electromagnetic fields/pulses and radar used in the first Gulf War. He stated that there was a small group of civilian researchers who developed cancers from the early devices. He stated, however, there was not much research and data in this area. Dr. Steele stated that she had heard from soldiers in Air Force units that believe that radar/microwave exposures on their bases had adversely affected them. Mr. Robinson stated that if an individual gets in front of one of these devices, it would burn their skin.

Ms. Val-Hammack suggested that the Committee look at non-lethal weaponry, and look at the issue from an industrial hygiene point of view. She also asked the Committee to look at Gulf War illness in relation to dental disease, including talking with civilian dentists about their observations of veterans' dental hygiene. Dr. Golomb noted that veterans are only eligible for VA dental care if they have a 100% service connection. She stated that rates of periodontal diseases should be acquired in some manner. Dr. Steele stated that this information would only be available from symptom-reporting in the registry and epidemiologic studies. Mr. Robinson stated this was a situation similar to VA's collection of birth defect information.

Dr. Haley asked if the Committee felt it had sufficiently addressed the issue of birth defects. Dr. Steele noted the birth defect chapter in the Committee's 2004 report, and asked for input as to whether additional information was now known.

Mr. Albert Donnay suggested that the Committee review carbon monoxide emissions from weapons as a possible exposure of concern. Dr. Steele asked the Committee for input on this potential exposure. She

noted that, in the Gulf War literature, handling munitions or being in combat have not appeared to be risk factors. Mr. Donnay noted that Navy personnel had symptoms, and had been firing large weapons from their ships. Chairman Binns noted that the Committee needed to fulfill its obligation to look at all exposures, but needed to work within limitations and focus/prioritize sources of concern when it comes to the large multisymptom chronic illnesses affecting many Gulf War veterans. Dr. Golomb agreed that carbon monoxide emissions need further research, but noted that this exposure was not unique to the Gulf War.

Dr. Steele reminded the Committee that the articles listed in their monthly updates were available for their review, and encouraged them to do so. Chairman Binns encouraged the Committee members to remain up-to-date on the published literature in this area.

Public Comment – Day 3

Chairman Binns opened the floor to public comment.

Mr. Donnay spoke to the Committee. He distributed three handouts to the Committee pertaining to CFS and MCS. He asked that the Committee recommend more research into genetic polymorphisms for these conditions and an increase in clinical screening for these conditions by VA physicians. He stated that he was pleased to hear Dr. Haley would be starting a study characterizing Gulf War veterans, with controls, by all available case definitions and reporting his results in those terms.

Ms. Nichols spoke to the Committee. She noted that veteran service organizations would be convening in the coming months for their annual meetings, and resolutions should be put forth concerning the Committee's work. She informed the Committee that Janyce Brown, the wife of a Gulf War veteran who had worked tirelessly to bring the issue of leishmaniasis to the forefront, had passed away recently.

Ms. Val-Hammack spoke to the Committee. She stated that Mrs. Brown had worked hard to document that visceral leishmaniasis was an issue for Gulf War veterans and their families. She noted that the Gulf War veterans' multiple sclerosis support group had been growing in numbers. She suggested that the Committee look at obtaining the data on the numbers of Gulf War veterans with multiple sclerosis.

Chairman Binns thanked everyone for their participation in the meeting.

The meeting adjourned at 12:30 p.m.