Research Advisory Committee on Gulf War Veterans' Illnesses

April 24-25, 2007, Committee Meeting Minutes

U.S. Department of Veterans Affairs
Washington, DC

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 24-25, 2007, meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses.

_____

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

Table of Contents

Attendance Record

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

Committee Consultant
Jack Melling

Committee Staff
Barbara LaClair
Laura Palmer

Designated Federal Officer
William Goldberg

Guest Speakers
Julia Golier
Janet Harris
Kristen Heaton
Douglas Wallace

Abbreviations

AChE	Acetylcholinesterase
ACTH	Adrenocorticotropic hormone
ALS	Amyotrophic lateral sclerosis
ATSDR	Agency for Toxic Substances and Disease Registry
AVA	Anthrax vaccine adsorbed
CCEP	Comprehensive Clinical Evaluation Program
CDC	U.S. Centers for Disease Control and Prevention
CDMRP	Congressionally Directed Medical Research Programs
CFS	Chronic fatigue syndrome
CoQ10	Coenzyme Q10
CRADO	Chief Research and Development Officer (VA)
CRF/CRH	Corticotrophin releasing factor/hormone
DU	Depleted uranium
DOD	U.S. Department of Defense
EEG	Electroencephalogram
EPA	U.S. Environmental Protection Agency
FDA	U.S. Food and Drug Administration
FY	Fiscal year
GWVIRP	Gulf War Veterans' Illnesses Research Program (DOD - CDMRP)
GWVIS	Gulf War Veterans' Information System
HPA	Hypothalamic-pituitary-adrenal axis
IOM	Institute of Medicine
LHON	Leber's hereditary optic neuropathy
MCS	Multiple chemical sensitivity
Mn-SOD	Manganese superoxide dismutase
MRI	Magnetic resonance imaging
MS	Multiple sclerosis
mtDNA	Mitochondrial DNA
NIH	National Institutes of Health
OEF	Operation Enduring Freedom
OIF	Operation Iraqi Freedom
ORD	Office of Research and Development (VA)
PB	Pyridostigmine bromide
PTSD	Posttraumatic stress disorder
RAC-GWVI	Research Advisory Committee on Gulf War Veterans' Illnesses
RFA	Request for applications
ROS	Reactive oxygen species
UC Irvine	University of California at Irvine

UK	United Kingdom
UTSW	University of Texas Southwestern School of Medicine
VA	U.S. Department of Veterans Affairs

Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses
April 24-25, 2007
VA Headquarters, 810 Vermont Ave., N.W., Room 230
Washington, D.C.

Agenda

Tuesday, April 24, 2007

8:00 – 8:30	Informal gathering, coffee	
8:30 – 8:35	Welcome, introductory remarks	Mr. Jim Binns, Chairman Res Adv Cmte Gulf War Illnesses
8:35 – 9:30	Oxidation, mitochondrial injury, and illness in Gulf War veterans	Dr. Beatrice Golomb School of Medicine, Univ. of California at San Diego
9:30 – 10:45	Mitochondrial paradigm for degenerative and metabolic diseases, aging and cancer: a critical interface between genes and environment	Dr. Douglas Wallace Center for Molecular and Mitochondrial Medicine and Genetics, Univ. of California at Irvine
10:45 – 11:00	Break	
11:00 – 11:45	Questions & answers / discussion re: mitochondrial injury	
11:45 – 12:45	Lunch	
12:45 – 1:35	Neuroendocrine functioning in Gulf War veterans: relationship to chronic health symptoms	Dr. Julia Golier Bronx VA Medical Center
1:35 – 2:25	Neuropsychological and neuroanatomical findings in 1991 Gulf War veterans with estimated low-level exposures to sarin and cyclosarin	Dr. Kristin Heaton US Army Research Institute of Environmental Medicine
2:25 – 2:40	Break	
2:40 – 4:30	Committee discussion: 2007 RAC-GWVI report	Dr. Lea Steele Res Adv Cmte Gulf War Illnesses
4:30 – 5:00	Public comment	

Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses
April 24-25, 2007
VA Headquarters, 810 Vermont Ave., N.W., Room 230
Washington, D.C.

Agenda
Wednesday, April 25, 2007

8:00 – 8:30	Informal gathering, coffee	
8:30 – 10:00	Committee discussion: 2007 RAC-GWVI report	Dr. Lea Steele Res Adv Cmte Gulf War Illnesses
10:00 – 10:15	Break	
10:15 – 11:00	VA Office of Research and Development update on Gulf War illness-related research activities	Dr. William Goldberg VA Office of Research and Development
11:00 – 11:30	DoD Congressionally-Directed Medical Research Program (CDMRP) progress report	Col. Janet Harris, Ph.D. Director, U.S. Army CDMRP
11:30 – 12:30	Lunch	
12:30 – 1:30	Committee Business	
1:30 – 2:00	Public comment	
2:00	Adjourn	

The April 24-25, 2007 meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses was held in Room 230 of the U.S. Department of Veterans Affairs (VA) Headquarters, 810 Vermont Ave., N.W., Washington, D.C.

Welcome, introductions, and opening remarks

James H. Binns, Jr., Chairman

Chairman James Binns called the meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses (hereinafter referred to as the "Committee") to order at 8:35 a.m. He welcomed Committee members, visiting scientists, VA staff and members of the public. He noted that the meeting's agenda had been slightly modified because Dr. Robert Haley would not be able to attend and would not report on the status of the University of Texas Southwestern (UTSW) Gulf War Illnesses research program. Chairman Binns noted that two UTSW researchers were in attendance: Dr. John Hart, a neuropsychologist and specialist in magnetic resonance imaging (MRI) research, and Dr. Matthew Goldberg, who headed a UTSW mitochondrial research program. Chairman Binns stated that, due to this agenda change, the meeting would likely finish earlier than planned the following afternoon, depending on how long the Committee's discussion on report recommendations lasted.

Chairman Binns noted that there was a film crew present, which would be filming certain portions of the day's meeting. The crew's main objective was to film a Gulf War veteran attending the meeting who was featured in their documentary on Gulf War veterans. The film crew had indicated that they would ask permission of anyone before filming them.

Chairman Binns announced that he just learned that VA Secretary R. James Nicholson had reappointed Dr. Beatrice Golomb, Ms. Marguerite Knox, Mr. Steve Smithson and Dr. Lea Steele to the Committee. In addition, Dr. Roberta White, who is with the Boston University School of Public Health and a long-time researcher in Gulf War veterans' illnesses, was appointed to the Committee. He indicated that Dr. White could not be at the meeting because of the late notice of the announcement.

Chairman Binns introduced Dr. Golomb and thanked her for arranging the morning's program. He noted that Dr. Golomb had long been interested in Gulf War illnesses research in relation to mitochondrial injury and had arranged for an extraordinary presentation on this topic.

Oxidative Stress, Mitochondria and Illness in Gulf War Veterans: A Hypothesis

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

Dr. Golomb gave an overview of how environmental exposures experienced by Gulf War veterans may have induced damage via oxidative stress and mitochondrial dysfunction, resulting in the illnesses evidenced in these veterans today. (See Appendix – Presentation 1.) Dr. Golomb noted her pleasure at having Dr. Douglas Wallace, Director, Center for Molecular and Mitochondrial Medicine and Genetics, University of California at Irvine, speak on this topic.

Chairman Binns indicated that general discussion of the issues raised by Dr. Golomb would occur following Dr. Wallace's presentation. However, he invited Committee members to ask Dr. Golomb if they had any specific questions to clarify her presentation.

Dr. Floyd Bloom, a Committee member, asked Dr. Golomb to discuss the process by which mitochondrial DNA (mtDNA) damage can become self-sustaining. Dr. Golomb stated that during the process of generating energy from oxygen, reactive oxygen species (ROS) are "thrown off" and as mutations accrue, even more ROS may be produced. These ROS, in turn, injure mtDNA, which results in more ROS.

Dr. Mary Nettleman, a Committee member, asked Dr. Golomb how vaccines might cause oxidative stress in an individual. Dr. Golomb stated that vaccines were reactogenic and produce local inflammation. Some studies have shown increased markers of oxidative stress in relation to vaccines. Inflammation itself often has oxidation as one of its primary mechanisms. Thus, local inflammation may lead to an increase in circulating oxidative stress markers. Dr. Nettleman asked if there was a way to look for direct evidence of this damage, as one would expect the most affected individuals would have the most damaged mitochondria. Dr. Golomb stated that there were methods, but these had not been applied with respect to Gulf War veterans because of expense. She indicated that she had applied for funding to study this theory, but with limited funds available in that funding cycle, it had not been granted. She discussed 31-phosphorous magnetic resonance spectroscopy and muscle biopsies as possible ways to determine whether mtDNA damage had occurred.

Dr. Lea Steele, Committee scientific director and member, noted that several things can cause ROS, and then asked Dr. Golomb if there was something particular about acetylcholinesterase (AChE) inhibitors that might lead to increased production of ROS. Dr. Golomb stated that if the question is why would ROS be particularly increased, that it may relate to the degree of oxidative stress. It may also be explained by the areas where ROS localize, and these differ from agent to agent. AChE inhibitors localize to brain and muscle areas. The level of exposure also plays a role.

Dr. Steele asked if there had been any studies that looked at mitochondrial damage in individuals with other multisymptom illnesses. Dr. Golomb stated that there had been DNA studies looking at chronic fatigue syndrome (CFS) patients. They found several different groups of abnormalities in these patients' nuclear DNA. Dr. Golomb noted that many mitochondrial aspects are coded by nuclear DNA. The CFS patients were placed into four groups with two groups associated with mitochondrial-related markers. She stated that there were also instances where CFS and fibromyalgia have been shown to have a mitochondrial etiology. She also noted that many people with mitochondrial problems will have a difficult time getting a diagnosis because most facilities don't have the ability to do the necessary testing. She indicated that one report had found that coenzyme Q10 (CoQ10) provided the greatest benefit for CFS from a group of treatments.

Dr. Clauw, a Committee member, asked Dr. Golomb about the source of the research to which she referred. Dr. Golomb stated that the information had been presented to the Committee by a speaker at a previous meeting. Dr. Steele commented that the Centers for Disease Control (CDC) genomic study in CFS patients had identified patient subgroups. Dr. Clauw commented that this study didn't find that this was a mitochondrial myopathy. Dr. Golomb stated she wasn't implying that the study identified CFS as a mitochondrial myopathy, but was providing an example of a study that had provided evidence of a connection of mitochondrial pathology to CFS.

Mr. Anthony Hardie, a Committee member, asked why Dr. Golomb had identified CoQ10 as a potential treatment when there were many naturally-occurring antioxidants. Dr. Golomb stated that she had selected it for a couple of reasons; including the fact that it is lipophilic and an electron carrier in the mitochondria so it helps with mitochondria generation. Also, most high doses of antioxidants are pro-oxidant. While this may be true with CoQ10, high doses of CoQ10 can increase concentrations of

available Vitamin C, Vitamin E, and carotenoids. The literature has been more favorable with CoQ10, and this may be because it has been studied more than other similar compounds.

Dr. Jack Melling, a consultant to the Committee, asked how feasible it would be to design a study or studies that could test the hypothesis proposed by Dr. Golomb. Dr. Golomb stated that she believed it was possible and had submitted such a research grant proposal. While it had not been funded, she didn't believe it was due to design, but rather to cost.

Dr. Bill Meggs, a Committee member, asked: (1) where endogenous CoQ10 enzyme was produced; and (2) if the natural decline in this enzyme with age was related to oxidative stress in the genes that make the endogenous CoQ10. Dr. Golomb stated that it was coded by nuclear DNA, and that she believed it was made in every cell.

Dr. John Hart, an audience member who is with the University of Texas Southwestern School of Medicine, noted that in the neuropsychiatric field there were several genes that are considered susceptibility or risk factors. He asked if there were any genetic markers, not necessarily mitochondrial in nature, that might cause an individual to be predisposed to a more pronounced effect from this type of damage. This would add to the variability factor. Dr. Golomb thought there would be a wide range, noting that there are enzymes that detoxify oxidative stressors. She deferred specific identification of these markers to Dr. Wallace.

Chairman Binns thanked Dr. Golomb.

Chairman Binns introduced Dr. Wallace.

A Mitochondrial Paradigm for Degenerative and Metabolic Diseases, Cancer, and Aging: Interface between Genes & Environment & a Paradigm for the Gulf War Syndrome.

Douglas C. Wallace, PhD
Director, Center for Molecular and Mitochondrial Medicine and Genetics,
University of California at Irvine

Dr. Wallace gave an overview of how mutations in the mitochondrial genome may cause various chronic diseases and how this may relate to the condition affecting ill Gulf War veterans. (See Appendix – Presentation 2.)

The meeting recessed at 10:48 a.m. for a break.

The meeting reconvened at 11:09 a.m.

Chairman Binns opened the discussion to Committee members.

Dr. Bloom stated that he found Dr. Wallace's presentation fascinating. He wondered, if this theory was presumed to be an explanation for Gulf War illnesses, what it might suggest with respect to possible treatments. Dr. Golomb stated that to determine whether this was a process related to Gulf War illness, one might use magnetic resonance spectroscopy, phosphocreatinine recovery after exercise, and biopsy studies of muscle that looked at mitochondrial complex function, mitochondrial density, CoQ10 redox, etc. Dr. Bloom noted that these would produce correlation findings and Dr. Golomb concurred, indicating that it would be useful to establish whether mitochondrial pathology correlated with illness. One could also look at treatments known to influence mitochondria, with the caveat that these also affect other things.

Dr. Wallace commented that Dr. Bloom's question was excellent and one that he is often asked. Dr. Wallace has been working on Alzheimer's disease as a mitochondrial disease for many years. His team has now shown in Alzheimer's patients, as well as in unpublished work on Down syndrome patients with premature dementia, that these patients have greatly increased levels of somatic mitotic mutations as the dementia progresses. But again, all of this is correlation. It is difficult in a human study to do anything but achieve correlation. The center run by Dr. Wallace at the University of California at Irvine (UC Irvine) has its own clinical program, research program, and mouse genetics program. This is because to prove causal relationships, one has to fulfill Koch's postulate. Because the mitochondrion is a bacterium, one has the possibility of doing just this, i.e., introduce a mutant bacterium into the female germ line of an experimental animal. If that mutant bacterium created or recapitulated the symptoms of interest, one would assume that they were causal. The UC Irvine team has been working on a system to introduce a maternally-inherited mutation into mice. While he can not ask the mice how they "feel," the mice are developing distinct symptoms.

Dr. Golomb stated that one could also introduce the related exposures and look for objective markers associated with mitochondrial dysfunction, and then see if these objective markers are shared with people who report illness. She noted, however, that there weren't necessarily good objective markers in people for the symptoms.

Dr. Wallace said that they have created several types of mice with different mitochondrial mutations. Initially, they focused on the nuclear genome. Now they have mutations that affect energy transduction, and the permeability transition for apoptosis and ROS production. They are also interested in environmental intoxication. They take an array of their mutations with the different mitochondrial systems and challenge it with different environmental toxicants. If the mitochondria are involved, they would expect the animal with the impaired system to be more sensitive. Some of his team's unpublished work is looking at why chronic alcoholics are more prone to acute respiratory failure. One hypothesis is that there is that there is a depletion of glutathione in the lungs. They have created a heterozygous mouse strain to test this hypothesis.

Dr. Meggs noted that one aspect of several syndromes related to Gulf War illnesses, e.g., sick building syndrome, is that the individuals have fixed neurological disabilities. However, they also have disabilities that wax and wane with subsequent exposures. Dr. Meggs noted that Gulf War veterans also have "good" days and "bad" days, and asked if there was a way to incorporate the variability of symptoms associated with subsequent exposures to chemicals into this model. Dr. Golomb stated that when one is exposed to a new oxidative stressor it affects things besides DNA (e.g., proteins, lipids, etc) which can in turn affect mitochondrial function. There is the potential, if those effects are strong enough, for the increase in ROS to perpetuate additional damage. Dr. Wallace agreed and indicated that cells can go through a progressive change. Initially, one can accumulate up to 60% severely damaged mtDNA before one will begin to see gross symptomatology. Most of the quantitative symptoms are primarily due to cell loss. One doesn't see a movement disorder primarily in relation to an energy deficiency. It is likely due to a reduction in dopaminergic neuron numbers. There is an intermediate stage where the cells aren't dead but are energetically impaired. He discussed their findings in patients with Leber's Hereditary Optic Neuropathy (LHON), in which patients see fluctuating loss in vision. They don't know what is going on in at this stage in the retinal ganglia cells, but believe the energy deficiency is cycling through its own inhibition or environmental effectors. When the ROS damage is significant enough, the individuals are permanently blinded. However, there appears to be an intermediate stage where the cells are still there, but are energetically deprived.

Dr. Meggs noted that there was a famous case of LHON in workers compensation law in which the individual had the disease but went blind temporarily, due to an occupational solvent exposure, which is known to damage vision. In this case, the individual won the case because the court held that, despite having a preexisting condition, the occupational exposure pushed him over the edge. He wondered if this might be a scientific explanation for this highly controversial decision. Dr. Wallace commented that one of the families in their LHON study had lived close to a military toxic waste dump. The daughter went blind at the age of six, which was the youngest reported case of acute onset LHON that he had seen. He noted this was anecdotal and they didn't know whether there was a secondary environmental intoxication. However, it was worth considering.

Dr. Golomb commented that in her own statin research, they have received reports of fluctuating eyesight depending on whether the patient is on or off the statin drug. She noted that statins reduce CoQ10. This condition, i.e. early macular degeneration, has been reversed with an early introduction of an antioxidant cocktail, which included CoQ10, omega-3 fatty acids, etc.

Dr. Wallace noted that he was a "mitochondriac." He acknowledged that burden of proof depends on one's perspective of the problem. He is strongly convinced that this paradigm is a correct one. He acknowledged that others might look at this experimental data to differently. Macular degeneration is an area they are seriously researching. The prevailing view is that it is not a mitochondrial disease. However, he believes there is good evidence to support that it is. Part of the problem of proving inherited mitochondrial disease is that the burden of proof is excessive compared with disease inherited in a Mendelian pattern. Their experimental paradigms are antithetical to the prevailing Mendelian paradigm, so people sometimes don't understand or accept their burden of proof. No amount of evidence will convince some people that a disease is mitochondrial in nature. He had spent the last 37 years trying to provide overwhelming proof of this process, not only correlative but causal evidence, and they will continue to do that. However, he believed that there was enough evidence, even though it was only from a few labs, that indicated this was a justifiable new way to look at this type of complex problem.

Dr. Meggs asked, if one accepted the hypothesis that ill Gulf War veterans' mitochondria had been damaged, what treatments could be suggested for further scientific study. Dr. Wallace stated that he would like to go back to the question of what would be the study to provide support for this hypothesis' validity. This would establish the dependent variables on which one will assess the therapeutic or clinical outcomes. Dr. Golomb and he had discussed a few options, with one suggestion being to look at mtDNA haplotypes in individuals exposed to the same environments but having differential outcomes. According to this hypothesis, if specific variations increase or decrease one's risk, one might see a similar association as that seen in Parkinson's disease. If this looked promising, then needle biopsies might be useful to quantify mtDNA mutation levels. He stated that they also had a mitochondrial expression array chip that looked at suppression of function on a thousand known mitochondrial function genes. He added that the physiological variables mentioned by Dr. Golomb would also be good outcome variables. Once these data were in place and could be evaluated, possible treatments could be explored. Dr. Golomb agreed. She also thought there was hope that there could be amelioration of symptoms. For instance, in terms of energetic deficiency, CoQ10 had been reported to "bypass" a variety of meta-causal mtDNA mutations and, in a sense, allow the cell to produce ATP. There are reports in the literature that CoQ10 partially improved muscle pain, headaches, shortness of breath, along with a variety of other symptoms that are reported in Gulf War veterans. She did not believe that there would be complete reversal of symptoms, but there was a chance of partial mitigation.

Dr. Wallace stated that all of the things that they currently used in the UC Irvine clinic, e.g., CoQ10, succinate, etc., are actually weak interventions. The problem that they have run into over the past 20 years with therapeutics is that few drug companies will consider producing more robust options. The

drug companies are designed to have the "key lock" paradigm for drug development. The idea of a systemic drug to change the physiology of the individuals is not only difficult to do, but it is impossible to get through the U.S. Food and Drug Agency (FDA) because of the lack of outcome variables for specific clinical phenotypes. The FDA can't evaluate a multisystem, age-related, chronic degenerative condition. His group has been using a *Drosophila* sp. model and has identified compounds that alter adenylyl cyclase levels, and therefore affect the ratio of ATP to ROS production. The mitochondrial-retarded catalytic antioxidants have great promise because they completely reverse symptoms, not only in Drosophila but in their mouse models with mitochondrial disease. He did not see any hope now though of getting anyone to take these drugs to a place that can get them to Gulf War veterans. There were real alternatives, but no real way to move them forward.

Dr. Steele asked about regionalization of the effect of mitochondrial function. For example, if a needle biopsy was performed, where would it be performed? If it was taken in the muscle, would it indicate whether anything was occurring in the brain? Dr. Golomb stated that if an individual had muscle symptoms, one would look in the muscle. However, because of the issues discussed by Dr. Wallace, there could be heterogeneity wherein one might have mtDNA in one area that is vulnerable to the added oxidative stress. But there was no absolute certainty that pathology in one organ would affect cell energy in another organ. Dr. Wallace stated that they were confronted with this issue every day. It reminded him of the joke of the individual who lost his keys on a hill at nighttime, so he was looking under the lamp post. When someone asked him what he was looking for, he told them that he lost his keys. They then asked him where did he lose them, and he indicated that he lost them somewhere over the hill. When asked why he was looking under the lamp post, he replied that the light was better. The problem is that you can only look where you can look. So they have to look at surrogates. They can't do a brain or retinal biopsy. Muscle turns out to be a good post-mitotic tissue, which is a surrogate for somatic damage. Dr. Wallace said that Dr. Golomb was right in saying that mitochondrial variation in the brain is not necessarily the same as in the muscle. However, if one has systemic oxidative stress that has damaged your mtDNA, a signature should be seen in both the muscle and the brain. They have also been experimenting with urinary tract epithelial cells because they are more stable, i.e., less mitotic. The blood is not a good place to look because of the presence of stem cells. If there is a severe mitochondrial mutation in some bone marrow stem cells but not others, the ones with the mutation are "killed" and the ones that don't have a mutation come to predominate. Thus, the blood is a bad indicator of tissue heteroplasmy because there is selection against deleterious mutations in the stem cells. This is why so many people miss mitochondrial disease because they always assume, as the Mendelian paradigm would predict, that the blood nuclear genome would be the same as the muscle genome. Heteroplasmy eliminates this. However, for extreme levels of oxidative stress, there may be enough mitochondrial mutations in the blood for detection.

Dr. Clauw stated that all of the mitochondrial disorders that he was aware of and that had been discussed that day were characterized by objective abnormalities, either in neurological function or something that could be measured. He asked if Dr. Wallace would be concerned if he knew that the two case-control neurological function studies found no objective differences between deployed and nondeployed Gulf War veterans. Dr. Steele added that that there were no peripheral differences, to which Dr. Clauw agreed. Dr. Clauw stated that he would consider the possibility of a mitochondrial problem in a patient if he saw muscle weakness, nerve damage, EMG or nerve conduction abnormalities, etc. He asked if Dr. Wallace could identify a disease that is not characterized by objective abnormalities in neurologic function, but where mitochondrial damage has been definitely shown to play a role.

Dr. Wallace replied that he might not be able to completely answer the question in a way that would satisfy Dr. Clauw. The symptoms mentioned by Dr. Clauw were certainly symptoms that some mitochondrial disease patients have and, if muscle biopsies are done, there might be presumptive

evidence that there is mitochondrial disease. However, take a case where you have a child perfectly normal with no signs of any problem, who dies at ten months of age with sudden onset of progressive loss of function. They get a sample of tissue and discover a tRNA cystine mutation in the patient. This disease does not have a label or fit with any of the well-characterized differential diagnoses, but it killed the patient. The patient didn't have well-defined red fibers or abnormal mitochondria. Dr. Wallace's group is also actively researching asthma, which is considered a chronic inflammatory disease. Dr. Wallace agreed that it was a chronic inflammatory disease, but noted that mitochondrial ROS activates NF-kappa B, changing the chromatin structure, which turns on the cytokines. The cytokines are systemically distributed into the body, which in turn produces a cascade that affects mitochondrial function.

Dr. Wallace said that his point was that, if one is limited to established diagnoses as the only kind of diseases that can be mitochondrial, one could never ask if a new array of clinical symptoms might be viewed in relation to the same pathophysiological mechanism. The problem is that the concept of a differential diagnosis that is taught to medical students, which is useful in many areas, is limited for the multisystem, age-related, degenerative diseases. This is why he, as a clinical geneticist, has a hard time defining the inheritance of depression, schizophrenia, etc. Defining the clinical endpoint that is associated with a stochastic disease process is assuming, to begin with, that it is going to be Mendelian, by definition. He stated that there is a stochastic genetics that defies the concept of the differential diagnosis. As long as this clinical paradigm is used, he would not be able to answer Dr. Clauw's question.

Dr. Clauw stated that Dr. Wallace had done a wonderful job convincing him that Mendelian genetics paradigm is too narrow and that mitochondria play an incredibly important role in all functions of the body. Thus, he wondered if it was possible or whether there was a known disease where mitochondria were damaged to the extent that they would cause disease, but an extensive neurological evaluation would not reveal any abnormalities. He noted that he studies fibromyalgia and so assumes nothing. Every hypothesis is a plausible hypothesis in this spectrum of illness.

Dr. Wallace stated that the answer to Dr. Clauw's question was "yes." For example, tRNA 3243 mutation was a well-defined mutation that was found in one of 4,500 people in the world. It is by far the most common known nucleotide change that is pathogenic. In the pedigree where the most common complaint is migraines, the second compliant is Type II diabetes. The third more common compliant is children who die of Leigh's syndrome, i.e., massive basal ganglia degeneration. Individuals with a low percentage of mutation (below 30%) have absolutely no detectable neurological disease. Dr. Wallace stated that the pathology is not detected by a thorough neurological exam, but rather through other clinical tests. Even so, they are confronted with patients with known maternal lineage mutations that have complaints, but are "soft" within the range of normal variation of many of these parameters. He stated that the question was then what is the source of the normal variation. He believed that much of the Gaussian curve of all of these clinical tests was due to mitochondrial haplotype variability in the background which has never been controlled. He thought it was difficult to find people on the edges of the normal range and be confident that they are not abnormal because "abnormal" is defined by the "normal" population. What he might find to be a maternal pedigree, others may see no inherited pattern in relation to the clinical signs.

Dr. Golomb added that her presentation had included an example of an inherited mitochondrial neurological condition that was expressed at 3 years of age in one member of the family, but at 70 years of age in another member. The older member of the family had the mitochondrial mutation for a long time before there were objective neurological symptoms. Many patients who come to Dr. Wallace's clinic report that they have been to several physicians about their condition but are told it is psychogenic. This is an example of mitochondrial pathology that might or might not be expressed as objective, severe

neurological disease. There is an interim period where the "soft" signs are present, which may or may not progress to "hard" neurological signs.

Discussion followed about different studies involving neurological testing of Gulf War veterans and variation in autonomic function. Dr. Clauw stated that the issue of concern for him is that every disease known to be due to mitochondrial pathology is associated with objective abnormalities on an extensive neurological exam. Just because someone has an abnormality in their mitochondria doesn't mean that every mutation leads to a disease. Dr. Wallace described the case of a young boy who died of massive system failure at 10 months of age and had a large maternal pedigree, with every person being heteroplasmic. If these individuals walked in a doctor's office, they would be viewed as "normal." There are cases of mitochondrial DNA mutation where people have no overt symptoms at age 25-30, and this is the norm rather than the exception. His clinic is like a big "garbage bin," where physicians refer individuals for which they can't find answers. His research experience has led him to conclude that there is a strong correlation between the age of the individual and the number of "hard" observable symptoms. He provided an example of a patient with severe fibromyalgia who had a tRNA arginine mutation in her mitochondrial DNA and was heteroplasmic. Her son had approximately the same heteroplasmy, but there was nothing wrong with him. She had lost three children in-utero, and it might be surmised that these children had higher mutation percentages. If he had seen the patient when she was 20 years old, he would have thought she was 'normal." Presumably some stressors, perhaps multiple pregnancies, pushed her over a threshold to a debilitating, age/time-dependent decline of function.

Mr. Hardie commented that he had a close nonveteran friend who, at age 27, had subjective symptoms of memory loss and confusion. This resulted in a brain scan being performed, which showed nothing. Eleven and half months later, this individual had a seizure, was transported to a hospital and died six weeks later of a very aggressive form of brain cancer. This led him to wonder about MRIs and other tests. With respect to individuals with Parkinson's disease, he asked Dr. Wallace at what point did these individuals have the disease. Only when their symptoms became apparent? Or when they have subjective symptoms prior to having neurologically observable, objective symptoms? Dr. Wallace stated that this was the burning question in neurobiology. Formally, a patient has the classic symptoms of Parkinson's disease when 60% of his or her dopaminerigc neurons in the substantia nigra have been lost. Dr. Wallace believed, however, that the pathophysiology that results in the death of these neurons long predates the actual onset of symptoms. Thus, they are very interested in whether mitochondrial haplogroups at higher risk might be identified. At-risk pre-symptomatic individuals might be identified and placed on antioxidant therapies to protect their dopaminergic neurons. This provides an example of a conceptual framework for how these diseases work and how to address them. Although American medicine focuses primarily on acute interventional medicine, it would be preferable to move towards preventive therapies.

Dr. Mary Nettleman commented that she realized that the current paradigms, including Mendelian genetics, had worked well for a long time, but had only taken us so far. This is apparent when it comes to Gulf War illnesses, fibromyalgia, and other areas. The concept raised by Dr. Wallace was very important. She noted that it comes against a medical structure that wants proof using the old methods. She asked whether there was way to start small, in order to get preliminary evidence, to get things started. She wondered if heteroplasmy would completely blur the picture. Dr. Wallace stated that he could work with Dr. Golomb or other researchers to provide short-term and long-term goals in this area of research for Gulf War veterans. This would also generate some of the outcome variables needed to progress further. He encouraged that research in this area be undertaken.

Chairman Binns asked that discussion go around the Committee table one more time, with comments or questions for Drs. Wallace and Golomb.

Dr. Steele commented that her research had shown a subgroup of ill veterans having permethrin exposure as a strong risk factor. This was a surprise to them. Permethrin isn't an acetylcholinesterase inhibitor, but affects the cell's sodium channel, which had been mentioned by Dr. Wallace in his explanation of mitochondrial pathology. She wondered whether this action might be associated in some way with mitochondrial damage. Dr. Wallace stated that 70% of ATP is used to maintain ion gradients. He would not have a problem saying there might be an association, but he would have to look at each of the ion channels to develop a more factual basis for this conclusion. However, affecting ion channels have a big effect on mitochondria. Dr. Wallace discussed a specific genetic polymorphism that affects an individual's ability to manage calcium influx.

Dr. James O'Callaghan, a Committee member, stated that if one considered the mitochondrial paradigm from a neurotoxicological perspective, one would find several "mitochondriacs" that populate this discipline. This is due to accumulated evidence over 25 years that shows, by and large, that most neurotoxins end up being mitochondrial poisons. He added that adding a mitochondrial poison on top of a primary neurotoxic agent makes things worse. However, most of the preclinical and even clinical research has not shown that antioxidants or anti-inflammatory compounds make things better. Dr. Wallace stated that available antioxidants react with the oxygen radical, and both are destroyed. Therefore, looking at the mass action of that approach, one can calculate the rate of oxygen radicals generated by the mitochondria. Even if one just calculates the number of DNA hits that have been estimated through urinary excretion, there are three orders of magnitude more oxygen radicals than you could dose with antioxidants when you work on a one collision per oxygen radical basis. That is why they are careful to develop drugs that are catalysts. Nature did not give us any catalytic antioxidants, because if it did, the signal transduction between the mitochondria and the nucleus would be disrupted and the cells would not grow. Biology has created a balance and does not want to get rid of all oxygen radicals. Oxygen radicals are important for signal transduction. Thus, we have to be careful about how antioxidants are used. We aren't dealing with something that is bad. It is only bad in a certain context.

Mr. Hardie asked, if this hypothesis is correct, whether this would suggest that EDTA chelation might help alleviate the resulting symptoms. Dr. Wallace replied that there was no definitive answer to this question. There was anecdotal evidence and "soft" signs about whether EDTA chelation was good or bad. He thought one could construct a hypothesis that might make sense. An overload of calcium is bad for the mitochondria, and EDTA does bind calcium. Other divalent cations are much worse, e.g., manganese, chromium, arsenic, etc., because they add electrons to superoxides and in turn, inhibit the respiratory pathway. There is a lot of interest in whether oxidative stress can be modulating divalent cation levels. The evidence for this possibility comes from a disease called Friedreich's ataxia. This disease is due a genetic mutation causing a deficiency in the enzyme frataxin. Frataxin binds divalent cations, specifically iron to a very high extent. If one has reduced fratxin levels, symptoms can include diabetes, ataxia, cardiomyopathy, etc. The idea is that fraxtaxin, as a protein, keeps the divalent cations in a state where they don't contribute to converting the superoxidant hydrogen peroxide to superhydroxl radicals. With a reduction of frataxin, one gets the equivalent of a chronic, increased level of oxidative stress. There is substantial correlative evidence in the research of this disease that supports this idea, and evidence that analogs of CoQ10 are therapeutic. Dr. Wallace said again that he couldn't answer Mr. Hardie's question directly, but could make analogies that suggest it might be possible. However, Dr. Wallace did not think EDTA chelation was the best approach because some divalent cations are good, and this technique was not specific or discriminating with respect to the cations it affected.

Dr. Meggs commented that there were many anecdotal cases that supported the hypothesis being discussed with respect to Gulf War veterans. He noted a case described in Alison Johnson's book where a disabled Gulf War veteran with polysymptomatic disease, who had an organophosphate insecticide

exposure, "flipped" into amyotrophic lateral sclerosis (ALS). It was not known whether this was coincidental or not.

Dr. Meggs then mentioned that a European expert in chronic fatigue syndrome (CFS) had recently told him that mitochondrial dysfunction had been discounted as a viable hypothesis with respect to CFS. He asked Dr. Wallace for his thoughts on this. Dr. Wallace stated that he was unaware of this data and did not have a hard pathophysiological answer to sweep all of these patients into one category. However, one can look at these types of problems and create a tenable mitochondria dysfunction hypothesis that has testable predictions. Dr. Wallace was aware of only two studies that looked at fibromyalgia, chronic myositis, and chronic myalgia using the mtDNA paradigm to look at the issue in a rigorous way. These studies used muscle biopsies from the patients, and quantified the level of mtDNA somatic mutations. As he remembered, these studies had found an increase in the mtDNA damage in a variety of these situations. Again, these were correlative data. There are many things from which people are suffering. The question is what is causing the suffering, because only when we know what is causing the suffering might we intervene. His clinic is large, and the people who come to work for him are interested in the mitochondrial hypothesis. However, his first statement to every physician is that they rule out every other possible explanation before they will consider a mitochondrial hypothesis. This is because it is too easy to take weak data and assume it explains everything. This was different from him suggesting that experimental researchers look at this hypothesis. Creating specific mutations in mice and then quantifying their phenotypes was the only way he would be able to convince himself of a causal connection.

Dr. Bloom commented that, in his experience with mouse models of human neurodegenerative disorders, the mouse neuropathology replicated the human pathology. Alzheimer's disease is not Parkinson's disease, and Parkinson's disease is not Huntington's disease. He asked whether there was enough known about mitochondria in neural circuitry to explain those variants on the basis of heteroplasmy of mitochondria. Dr. Wallace remarked that the difference between a person with memory loss and a person with a movement disorder was the type of neuronal connection that was lost. A person with a movement disorder has primarily a basal ganglia problem. Progressive mental dementia is more often cortical in origin. Those neurons are different in their physiology, so dopaminergic neurons are the most commonly affected by mitochondrial dysfunction. This is because dopamine is turned over by monoamine oxidase, which is found in the mitochondrial outer membrane and uses the electron transport chain as reducing equivalents in producing hydrogen peroxide. Thus, it makes sense that dopaminergic neurons will be more sensitive to oxidative stress than corticoneurons. As to why some mitochondrial mutations cause optic atrophy while others cause basal ganglia degeneration, Dr. Wallace did not have a "hard" answer. This is something he would like to find the answer to himself. However, there are many clinical mutations that are known to affect different parts of the brain. So, they have "seen it", but they don't understand it.

Chairman Binns noted Dr. Wallace's discussion of resveratrol. He asked if resveratrol might offer a promising therapy. Dr. Wallace discussed the mechanism by which resveratrol interacted in the mitochondria. He did not think that resveratrol would be the panacea that people need because it would require too high a dose to obtain a consistent physiological outcome. He said that there was an effort to find more bio-accessible derivatives, i.e., ones that are absorbed more efficiently and disseminated through the blood-brain barrier. Pharmacological development is needed, and he was aware of candidate compounds in the pipeline. One of the problems with resveratrol and this group of compounds is that it is based on assumption that all oxygen radicals are bad. However, there is clear evidence that if the oxygen radicals are disrupted, there is fetal loss. This signal transduction is very important. He is not sure what the toxicity of these compounds will be in the long-term. There is great need for more empirical data, but

these compounds do show promise. He would not advocate that Gulf War veterans take resveratrol at this time.

Dr. Steele asked if the problem was the bioabsorption of the antioxidant. She had heard from several clinicians who were using high-dose IV antioxidants that had patients who swore that it put them "back on their feet." Dr. Wallace said that vitamins E and C were required for life. His added that one shouldn't overreact and get rid of all oxygen radicals without thinking of the implications. As far as why resveratrol is promising, it is already in red wine, so the FDA would not be too prohibitive of it. Its action also differs from vitamins E and C in that it affects gene expression to impact production of an antioxidant enzyme. Resveratrol upregulates manganese superoxide dismutase (Mn-SOD), which is an important mitochondrial antioxidant. Thus, this is catalytic and a good thing, i.e., upregulating mitochondrial biogenesis. It results in increased ATP production and fewer oxygen radicals. They have discovered that the estrogen receptor is in the mitochondrial matrix, and estrogen receptors directly regulate the specific activity of Mn-SOD. In cultured cells, the addition of estrogen can double the antioxidant potential from the mitochondria. This may be why women live, on average, 10 years longer than men. However, would it be a good idea to give male Gulf War veterans estrogen? Dr. Wallace said the answer was "no" and that although there are many possible approaches, implementing them would require more thought. Resveratrol was promising because it works at a regulatory level, and not at the one-one level of these antioxidants.

Chairman Binns noted Dr. Wallace's concern about the inherited aspects of this hypothesis. He asked if the types of mitochondrial abnormalities discussed, even if triggered by events during a person's lifetime, can be passed onto offspring. Dr. Wallace replied that there were three types of mitochondrial variation that were relevant: (1) ancient polymorphisms that are adaptive. These polymorphisms change people's baseline physiological state; (2) new mutations in the female germ line. These would be inherited mutations, and if deleterious, could produce a disease state; and (3) somatic mutations that occur in post-mitotic tissues, e.g., brain and heart muscle. This latter group is not inheritable. The problem is that if individuals are subjected to a systemic oxidative stress that damages their mitochondrial DNA and happened to be female, this could also create mutations in their primordial germ cells. These mutations could then create heritable mutations. This may account for the putative increase in neural tube defects that have been observed. For males, damage to the Sertoli cells, which help sperm to develop, may affect fertility levels. He hadn't been able to determine how this might explain the burning nature of semen though. He noted that the prostate blocks the respiratory chain and generates citrate. Citrate is important because it is the substrate that sperm mitochondria burn to run the sperm tail. One could alter the physiology of the prostate by somatic mutations. Males would not produce inherited defects, but damaged sperm resulting from this process could result in disease. Most of the "soft" problems probably wouldn't be inherited but the possibility of increased genetic risk cannot be ruled out.

Chairman Binns noted that the Committee had explored neuroinflammation as a mechanism that could underlie Gulf War illnesses. He asked what might be the relationship between this hypothesis and the mitochondrial injury hypothesis. Dr. Wallace stated that he did not have "hard" research data, but it is an area that they were actively pursuing. He discussed a maternal pedigree group seen at his clinic that had had severe chronic, infectious diseases. He had wanted to trace this family, but lost touch with them. He did not think adequate thought had been given to the role of mitochondrial variation in immune and inflammatory responses. The logic, however, is straightforward. A modest change in mitochondrial respiration rate, together with an excess of calories, will generate electrons and increase ROS production. One of the biggest correlates of asthma is obesity. Dr. Wallace noted that ROS activates NF-kappa B, which is the major proinflammatory effecter. It goes from the cytoplasm, activated by ROS, and turns on all the cytokines. There are several types of cytokines, many of which upregulate mitochondrial ROS production. So from his viewpoint, what is happening is this: an environmental challenge, such as an

oxidative stress, can affect the lungs by increasing production of mitochondrial ROS production. ROS production activates NF-kappa B, which turns on the cytokines. The cytokines are distributed systemically through the body and produce a cascade effect to uncouple mitochondria. Why? This is because the best innate immune response is to increase temperature. Uncoupling of mitochondria accomplishes this. But this also puts the cells at risk for energy deficiency and apoptosis. And this is what they think anaphylaxis is. He stated that nobody else would probably agree with this, but it is the only way he could make sense out of it.

Chairman Binns asked Dr. Matthew Goldberg, an audience member who directs a mitochondrial research program at UTSW, if he had any questions. Dr. Goldberg noted that the goal was to have enough mechanistic understanding of Gulf War illnesses to develop more targeted therapies. This begged the question of whether ROS is the "whole story." Could mitochondrial dysfunction manifest itself in Gulf War illness due to other aspects of mitochondrial physiology, e.g., calcium signaling, regulation of apoptosis, etc.? Or are ROS the "bulk of the story"? Dr. Golomb suggested that ROS might be a triggering phenomenon and that after the process is initiated, a full complement of mitochondrial pathologies could produce these effects. Dr. Goldberg asked where investigative efforts should then be directed. Is it worth exploring mitochondrial physiology broadly in terms of calcium signaling, apoptosis, etc.? Dr. Wallace urged, if this hypothesis were to be pursued, that the research not be focused in one center. One can't get the breadth of input needed relying on just one viewpoint. There are many interacting factors, requiring a variety of excellent investigators looking at ion channels, calcium signaling, ROS, and energy, using various techniques, e.g., P31-MRI, etc. The research monies should be distributed through some sort of R01 funding mechanism that is competed for on the basis of the quality of the science, and reviewed by a group of researchers who know the field. Until this is done, Dr. Goldberg's question will persist.

Chairman Binns thanked Drs. Wallace and Golomb for their presentations.

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

The meeting reconvened at 1:34 p.m.

Chairman Binns introduced Dr. Julia Golier.

Neuroendocrine Functioning in Gulf War Veterans: Relationship to Chronic Health Symptoms

Julia Golier, MD
Medical Director, PTSD program, VA Medical Center, Bronx, NY
Associate Professor of Psychiatry, Mount Sinai School of Medicine, New York, NY

Dr. Golier discussed her neuroendocrine research in Gulf War veterans with and without diagnosed psychiatric illnesses, including a review of their findings in relationship to environmental exposures during the war. (See Appendix – Presentation 3.) Overall, her findings indicated that hypothalamic-pituitary-adrenal (HPA) axis alterations were associated with chronic symptoms in Gulf War veterans, but were distinct from those associated with posttraumatic stress disorder (PTSD).

Dr. Golomb noted that Dr. Golier's findings might represent a positive adaptation because the veterans without PTSD were not more symptomatic in terms of other domains. Dr. Golier stated that it could be an adaptation to chronic activation of the hypothalamic-pituitary-adrenal (HPA) axis and enhanced negative feedback to achieve homeostasis. What is confusing about the data is that, on one hand, the deployed Gulf War veterans without psychiatric illness do not have greater physical symptoms than nondeployed veterans. However, on the other hand, the part that made her think it was clinically significant was the correlation between the symptoms and the HPA axis.

Dr. Clauw stated that his team had published articles over the years on HPA axis measures in fibromyalgia patients. In fibromyalgia patients with and without PTSD or depression, corticotropin releasing factor (CRF) levels in the spinal fluid are highly related to the level of pain at the time of testing. Classically, it was thought that PTSD and depression were driving these changes in the CRF. Also, three-day salivary cortisol levels were highly related to pain at time of testing but less so to other somatic symptoms. There wasn't much difference, overall, between fibromyalgia patients and normal controls. With regards to Dr. Golier's future studies, Dr. Clauw suggested carefully measuring pain and fatigue levels and using these as covariants to see if they were driving their results. He said that his group's original hypothesis had been that they would find more differences between fibromyalgia and controls or within the fibromyalgia group with and without the presence of PTSD and/or depression. This is not what they found. Pain is a stressor. It is the most common cause of postoperative high blood pressure. Until recently, though, it hasn't been considered a factor in driving some of these HPA axis findings.

Dr. Steele wondered whether Dr. Golier's current data could already address this. She noted that they had symptom measures and cortisol levels. Dr. Golier stated that the symptom measures were not assessed at the same time of the drawing of blood samples. Dr. Clauw commented that Dr. Golier had also probably inquired about the presence or absence of pain versus the severity of pain, which would be evaluated through pain diaries, etc. Dr. Golier stated this was correct.

Dr. Melling commented that, in terms of future studies, the "cut" made in this study essentially was Gulf War veterans with some evidence of PTSD. He suggested that groupings could be made with Gulf War veterans with no signs of Gulf War illnesses or PTSD. These veterans would be, in a sense, a Gulf War veterans control to put alongside their other control. He noted that another group could be Gulf War veterans with PTSD who do not exhibit multisymptom illnesses. Dr. Golier stated that they could find veterans with somatic symptoms but without psychological symptoms, and they could find them without somatic or psychological symptoms. However, it was difficult to find veterans with PTSD and no somatic symptoms. Dr. Melling commented that one of the Committee's 2004 report findings was that deployment stress could not account for the unexplained illnesses affecting Gulf War veterans. If Dr. Golier was in agreement with this finding, he thought it was important to reflect this in future studies.

Mr. Hardie asked whether Dr. Golier was able to see any difference in the cortisol levels and other findings of Gulf War veterans with PTSD compared with non-Gulf War veterans with PTSD. Dr. Golier stated that there were two things to consider. First, the absence of low cortisol levels in the PTSD group. There have been three other PTSD studies to date that looked at cortisol levels over a 24-hour period. Her group had done one study with Vietnam veterans and found a difference between veterans with PTSD and non-exposed, healthy men. Another study looked at abused women with PTSD and found that they had lower cortisol levels than the control group. The third study did not find the lower cortisol levels. Secondly, what is the meaning of the "normal" adrenocorticotropic hormone (ACTH) level in the Gulf War group with PTSD? She commented that questions arose as to whether these veterans were really "normal," or whether these levels were mixed with an effect seen in the exposed Gulf War groups without psychiatric illness, who had lower ACTH levels than the nonexposed group. It could be argued that the PTSD group actually had an elevated ACTH on top of the deployment effect but this is difficult to separate out.

Dr. O'Callaghan commented about the relationship of these findings with previously discussed neuroinflammatory issues and how it was a matter of continuous signal communication between the brain and the periphery. This process had been well described by Bruce McEwan. Dr. Golier commented that ideally these questions would be answered simultaneously. However, she had yet to see a chronic stress model with low ACTH levels. There have been findings of an absence of elevated ACTH levels, but not low levels. Dr. O'Callaghan also referred to Dr. Golier's mention of the cytokine hypothesis with respect to psychiatric disorders. He noted that the Committee had heard several overview presentations about how inflammatory disorders of the brain might relate to the overall multi-symptomatology of Gulf War illnesses.

Dr. Hart asked Dr. Golier if the ACTH and/or cortisol measures correlated with any of their memory or cognitive measures. Dr. Golier stated that the absolute levels of ACTH and cortisol did not correlate. However, the cortisol/ACTH ratio did associate with psychological and neuropsychological symptoms. It was somewhat confusing as to why there may be low ACTH and normal cortisol levels, because ACTH is the major regulator. Dr. Hart asked for Dr. Golier's thoughts about how deployment or exposure might change receptors or feedback mechanisms, and where this change might be, e.g. pituitary, adrenals, etc. Dr. Golier said she had hoped that those present might have some input along those lines. She noted that in animal models where there is an exposure combination of pyridostigmine bromide (PB) and low-levels of sarin, the hypothalamus is one of the target organs. Thus, it is possible this is a downstream manifestation of hypothalamic damage. There were no other data that could support this pattern, but it could explain lower CRH coming from the hypothalamus. Also, acetylcholinesterase inhibitors are very potent stimulators of the HPA axis. Dr. Hart asked if the veterans had autonomic complaints, e.g., dizziness, temperature regulation problems, etc. Dr. Golier stated that there were reports of dizziness; though she was not sure about temperature issues.

Dr. Steele commented that Dr. Golier's Gulf War veterans who didn't have PTSD appeared to be healthy controls. She noted that Drs. Roberta White's and Susan Proctor's group had done studies looking at symptom types as outcomes, in a similar manner as Dr. Golier. They had also published papers that looked at multisymptom illness and combinations of symptom types. She asked if Dr. Golier had ever "cut" her data in a similar manner. Dr. Golier stated that they did not have clinician-diagnosed chronic multisymptom illness but had used self-reports. If they were to "cut" the data by looking at chronic multisymptom illness, they would find increased cortisol suppression. Dr. Golier was not sure what the ACTH findings would be. Their current study is a 2x2 design where chronic multisymptom illness and PTSD are considered. Dr. Steele asked if all the deployed veterans in the study had experienced trauma during their deployment, or whether their findings were independent of this. Dr. Golier stated that this was one of the entry criteria to the study, which had not been hard to fulfill.

Chairman Binns thanked Dr. Golier

Chairman Binns introduced Dr. Kristin Heaton

Neuropsychological and Neuroanatomical Findings in 1991 GW Veterans with Estimated Low-level Exposures to Sarin and Cyclosarin

Dr. Kristin Heaton, PhD
US Army Research Institute of Environmental Medicine
Military Performance Division, Natick, MA

Dr. Heaton discussed her group's research showing less proficient neuropsychological performance and neuroanatomical differences in Gulf War veterans after possible low-level exposure to sarin and cyclosarin released during the 1991 demolition of the Khamisiyah ammunition depot. (See Appendix – Presentation 4.) This research suggested that exposure to low levels of sarin/cyclosarin might contribute to subtle white matter degradation that can be detected 8-10 years post-exposure.

Following Dr. Heaton's presentation, Dr. Meggs noted that the modeling of the Khamisiyah plume had been highly controversial. He asked if the control group was outside of all the different plume models. Dr. Heaton stated that, to her knowledge, they had not examined this. Dr. Golomb commented that if this was a null finding, this would be a bigger concern.

Dr. O'Callaghan asked Dr. Heaton if she could provide some background on the issue of how to normalize data and whether there was any controversy related to how their segmentation data would compare to Dr. Weimer's in the San Francisco Gulf War imaging research. Dr. Heaton stated she was not familiar with Dr. Weimer's segmentation data or program. She was only familiar with the program used in their study, which was in wide usage. She understood, though, that there were questions and concerns about various segmentation programs.

Dr. Steele asked whether Dr. Heaton and her group had used other self-reported exposure data in their modeling. Dr. Heaton stated that they had controlled for pesticide exposure during and post-deployment and the pattern of results had remained the same. Dr. Steele asked if they had looked at pesticide applicators versus those with no pesticide exposure to see if there was a similar decrement in white matter. Dr. Heaton stated that the numbers were too small, but agreed that this would be of interest. She added that a group at Boston University's Environmental Hazards Center was looking at effects of various pesticide exposures using neuroimaging techniques. Dr Steele noted that Dr. Proctor's study had reported no difference in cognitive function between those with chronic multisymptom illness and those without. She asked if Dr. Heaton could comment in relation to her study. Dr. Heaton replied that they had had not factored this into their linear analyses. Dr. Golomb asked if they had used self-reported chronic symptoms. Dr. Heaton replied that they had used objective cognitive data. All of these data were collected in 1994-1995, while the imaging data were collected in 2000-2001. Dr. Heaton noted that they did not have any information on what happened in the intervening time period and had not collected neurocognitive data when collecting the neuroimaging data. In hindsight, this would certainly have helped answer some questions.

Dr. Clauw asked if they had looked at the data in the first (Proctor) study with the linear trend model instead of the categorical model. He noted that she reported that it was using the linear trend model that the second study turned out "positive." Dr. Heaton stated that both approaches were used in the first study and resulted in the same findings, e.g., decrements in motor performance, etc.

Rev. Joel Graves, a Committee member, asked whether individuals with PTSD symptoms were excluded from the study. Dr. Heaton said that they were not, but that PTSD had been controlled for in the results. Rev. Graves commented that Mr. Keith Rhodes from the U.S. General Accounting Office had given a presentation to the Committee, showing that the Khamisiyah plume had been very different from the Central Intelligence Agency (CIA) and DoD models. He suggested that it might be helpful for Dr. Heaton to look at this model, as some individuals that she thought might be outside the Khamisiyah plume area might have actually been within it. Dr. Heaton stated that their study's "unexposed" group had been in Kuwait. Dr. Golomb suggested that an alternative design would be to evaluate individuals who were in both plumes compared to those who were in neither or only in one plume.

Rev Graves asked if there was a follow-up study planned to capture the status of this group today. Dr. Heaton said that she was no longer with VA and was not sure if there was planned follow-up with the Fort Devens cohort. The group's current study is looking at various pesticide exposures.

Chairman Binns stated that it was his understanding that there was further research being done in Boston with regards to Gulf War veterans, which would be published shortly. He thanked Dr. Heaton for her presentation. He noted that, while there had been studies showing the effects of low-dose sarin exposure in animals, this was the first published study showing effects in humans.

The meeting recessed at 3:15 p.m. for a break

The meeting reconvened at 3:31 p.m.

Committee discussion: 2007 RAC-GWVI report – Day 1

Dr. Steele outlined the topics that would be addressed in the 2007 RAC-GWVI report and led a discussion of recommendations for inclusion in the document. (See Appendix – Presentation 5.)

Chairman Binns commented that he had had concerns that because many of the current Committee members had not been on the Committee in 2004 and 2005 that it might be necessary to do two reports and reconvene the old panel. However, the officer in charge of VA advisory committees had indicated that it was common for turn-over of Committee members, and reports were routinely put together that involved periods of time when not all of the individuals were on the Committee. He stated that the decision was then made to highlight where Committee members could find this information if they were not present. If any members were uncomfortable supporting any recommendations due to the fact that they were not present for the earlier meetings, this would be made clear in the report in some fashion. He also asked that, while all of the recommendations have been or will be discussed in Committee meetings, the specific content of the report be closely held until the document is finalized and publicly released.

Chairman Binns asked Committee members to give their initial thoughts regarding the draft report.

Rev. Graves was impressed with the report, but wanted to ensure that his May 2006 presentation information was included in the chapter regarding nerve agents. Dr. Steele stated that there were plans to include it as part of the update on that topic.

Dr. O'Callaghan stated that the report informed him on many topics for which he was not present for discussion in 2004 and 2005. He felt that the overview of depleted uranium was very good. He noted the concern discussed about the effects of the oil well fire plumes. He wondered if there was an opportunity to dovetail future studies with the current interest within the U.S. Environmental Protection Agency

(EPA) in particulates. This might bring in researchers who are already conducting related research that is not currently directed at Gulf War veterans. As for the rest of the recommendations, Dr. O'Callaghan believed that they were on point.

Mr. Hardie commented that, when working to help implement the recommendations in the 2004 report, it helped to have a stand-alone table of contents that reflected the recommendations in bold. These recommendations were compelling, succinct, and in plain English. Any lay reader could understand these points. He would recommend that this be done again in the executive summary of this report. He also noted that he was pleased with the work of the Committee prior to his appointment and would have no problem supporting everything done by the Committee previously.

Mr. Adrian Atizado reiterated Mr. Hardie's comments with respect to the need to have the executive summary highlight the recommendations. This is the primary section of the document that would be used by Congress to understand the Committee's recommendations. He had reviewed many of the report's recommendations and agreed with them. He liked the progression of the document.

Dr. Golomb commented that she had not had the opportunity to review the document yet.

Dr. Meggs stated that he could sympathize and had faced similar time demands when the previous Committee report was been reviewed. He stated that he felt that Dr. Steele had done a fabulous job of summarizing the Committee's discussions on various topics. He felt that it was representative of what the Committee had covered and done. He did feel that the report should have a summary of how the Committee's report differs from the Institute of Medicine's (IOM's) reports. He noted that the Committee's focus had been different and had integrated animal studies into the discussion. He would also recommend that repetition of previous longitudinal studies, such as Dr. Heaton's cohort, be pursued to see if the individuals fell into three groups (got better, stabilized, got worse) and examine the exposure differences of these groups. He noted the need for more repeatable data. He stated that he liked the section on multiple chemical sensitivity (MCS) and the discussion of how chemicals can exacerbate all sorts of diagnosable conditions. He noted, however, that this point could be amplified a little more and that he was willing to help with this text. He noted that, with respect to treatments in this area, more research was needed on whether ongoing exposures can exacerbate and lead to the progression of this illness

Dr. Bloom stated that the four highest priority research topic recommendations made were logical, and he had no problem supporting them. He noted that implementation of these recommendations, however, would be harder than the text implies. He suggested that the report spell out some of research opportunities that should be undertaken. He noted that the case had to be made about the number of veterans who were experiencing these illnesses and whether the incidence has increased. Dr. Steele stated that the Committee had addressed this in its first report, noting that 25-30% of Gulf War veterans are symptomatic, over and above rates experienced by nondeployed veterans. She stated that this point would be stressed again in this report. Dr. Bloom agreed that this should be done. He commented that before sitting on the Committee, he was unaware of how Gulf War veterans' illnesses resembled other multisymptom complex diseases. This case needs to be made strongly if the Committee is to make recommendations that the treatments used for other multisymptom complex diseases be investigated with respect to Gulf War veterans.

Dr. Bloom commented that the research overview chapters used a floating standard related to the type of research cited. The report noted in places that some research had not been replicated, while in others, mention was made about studies that needed to be replicated. He felt that the Committee should identify studies that should be replicated for better understanding of the pathophysiology of this illness, which is a

step towards developing diagnostic markers to evaluate treatments. Dr. Steele asked if Dr. Bloom felt there was general vagueness on this, noting that she tried to show what had been found in one unreplicated study versus what had been found repeatedly in multiple studies. Dr. Bloom stated that this had been done, but also noted that many of the cited journals, in his opinion as a journal editor, were low-quality journals. He stated that to have something that is replicated in a low quality journal is almost the same as not being replicated at all. Dr. Golomb commented that this area of research had been much politicized and that early funding decisions were made in favor of researchers who had a particular viewpoint. This affected the pool of researchers who had published in the higher quality journals later in the process. Dr. Bloom stated that he was not disputing this, but until the science was published in better quality journals, the broad body of researchers was not likely to be as convinced of these findings. Dr. Golomb agreed with this point.

Dr. Bloom stated that, with respect to the identification of objective measures that distinguish veterans with Gulf War illness from healthy veterans, there were still several gaps between the types of findings described by Dr. Wallace in his mitochondria research and what had been observed in veterans. He did agree with Dr. Wallace's point that identifying biomarkers was the first step in assessing treatments that came along. He believed that this point should be made under this particular bullet in the report. Dr. Steele noted that the Committee had already referred to two different processes for identifying treatments: (1) empirical, i.e., looking at what is helpful for individuals with Gulf War illness or similar problems, and (2) identifying the specific pathophysiological processes affecting ill veterans and try to identify treatments that counter them. Dr. Bloom stated that this was very hard to do, with which Dr. Steele agreed. Chairman Binns commented that he understood Dr. Bloom's point was that identification of biomarkers was a prerequisite to being able to determine whether a treatment worked or not. Dr. Bloom said this was correct. One did not need to understand the mechanism if there was a biomarker that showed that one was on the road to improvement. In his field of mental health research, there was a group of drugs that had been discovered for the wrong reasons and applied to the wrong patient population. However, due to clever clinicians' observations, the drugs' better applications and proper patient populations were discovered. In some cases, they still don't understand why these drugs do and don't work, but there were a lot of people being helped.

Dr. Clauw stated that he agreed with a lot of what Dr. Bloom had just said. He noted that there were probably only a couple of things that the entire Committee would agree with, and some of these were different than previous reports, e.g., IOM. He noted that many of the early IOM reports were dismissive of this group of patients and of this spectrum of illness. They basically said these patients were reporting symptoms, or rather "complaints" as if they were not valid. He noted that that everyone on the RAC would agree that Gulf War veterans are really sick, that there are a lot of them and that they are not being helped right now. This was not a fault just of the VA system, but a fault of the entire medical system. This point needed to be stressed in the executive summary of the report. He stated that the Committee could "bicker" later as to why these veterans became sick. This is where he would disagree with many of the explanations presented. However, at the end of the day, what will distinguish the Committee's report from other reports is it's finding that these veterans are ill with legitimate problems that are not being addressed by the current system of health care. This is the major point that needs to be made to those responsible for appropriating more money. The nuances of the particular research should be left to the various study sections. Dr. Clauw believed that the Committee's report needed to be very clear and succinct in this regard. Dr. Steele commented that the report's outline had been morphing over the past year due to the issuance of other reports. She noted that these other reports were finding that there was no "unique" syndrome, but not stressing that these folks were really sick, that something needed to be done, and that they were sick as a result of their service. She envisioned this being conveyed in the introduction, and teased throughout the chapters, but hadn't settled on a way to convey that as forcefully

as it needed to be conveyed. Dr. Clauw added that, despite the fine tuning needed, that he felt that draft report was fantastic and that he agreed with most of what was in the document.

Dr. Nettleman commented that one of the primary goals should be to bring Gulf War illnesses back to the scientific stage. She thought that many people had been pushing it out of this setting. She thought that the report would have a political life, and that the executive summary should contain "sound" bites that could be picked up by the same newspapers that picked up the IOM report. This is not to be disrespectful to the IOM, but to highlight why the Committee thinks these illnesses are an important problem. She has come away from this process with the realization that science is on the verge of a new era, whether it be nanomedicine, cellular components, the understanding of inflammatory pathway, or system biology. We are on the verge of discovery. This discovery is what will give us the answer. We can't look backwards using Koch's postulates, and say it is nullified and there is no such illness. We have to look forward into the future. Dr. Nettleman felt that the draft report did provide a great overview of the literature that was pushing us into this new century. She also noted that treatments should be the Committee's number one priority. However, she wondered if the question was whether we were there yet or whether novel treatments still needed to be identified. Her impression from reading the draft report was that there were several candidates, but there was a need to put money into testing them. She believed though that money needed to be put into finding novel treatment candidates too.

From her review of the research presented, Dr. Nettleman commented that pyridostigmine bromide (PB) probably was not something one wanted to give to an individual every day of their deployment. She found the information with regards to its toxicity more compelling than the information for its benefits. She wasn't sure if this had been noted before, or if it had been so politically charged that such a statement would negate this report in certain circles. Dr. Steele stated that neurotoxins, such as PB and other acetylcholinesterase inhibitors and pesticides, had been grouped and addressed in the first report. Dr. Nettleman commented that she was making this comment on the data in the draft report, and wasn't sure if the Committee wanted to take this large of step. Dr. Golomb stated that there was some good news in that the U.S. and Israel has changed their policies so that while soldiers are still given PB packages, they are not given the order to take it unless there is significant evidence of soman use on the battlefield. She did not believe that the U.K. had similarly changed its policy regarding PB use.

Dr. Steele commented that Dr. Nettleman had mentioned on prior occasions that Gulf War illness had to be viewed as an entity, and that it happened to a large number of people after a common experience. Dr. Nettleman stated that the Committee had accepted this, but it was important that the report remind the public that this was the case. Dr. Nettleman concluded that the draft document was well-written and amazingly comprehensive.

Dr. Melling stated that he endorsed the point made about Gulf War illness as an entity. If we lose sight of this, a lot of the drive to understanding the treatments would be immediately displaced. In terms of recommendations, he thought that the importance of animal and in vivo models needed to be highlighted more. Looking forward, if there is to be a breakthrough, this research will lead to understanding the mechanisms of Gulf War illnesses. He wondered if it would make things clearer give higher priority to animal research. This might lay a better foundation for recommendations for future animal or tissue culture models. Dr. Steele noted that animal studies were addressed throughout the report, but asked if Dr. Melling was suggesting that these studies be addressed separately in relation to all the different exposures. Dr. Melling indicated this was the case and that this should then lead to a synthesis of findings. He found the importance of neurotoxic exposure compelling for two reasons: (1) the epidemiological data that highlighted it in the first place, and (2) the supporting evidence that came from numerous low-dose sarin, PB, etc., animal studies.

Chairman Binns thanked the Committee for the productive discussion. He stated that these comments would help make a stronger report. Further, this needed to be a document that somebody could look at the major findings on one page. Another thing that needed to be stressed was the number of veterans who are affected with Gulf War illnesses. He indicated that through his own recent dealings, he had come to realize that the magnitude of the problem has not been communicated clearly. He noted that veterans in general have recently moved back into public view. People are recommitting themselves to the importance of providing medical care to veterans who served in current wars. It is important to make these points clear to the scientists and general population.

Rev Graves commented that when President Bush was at Walter Reed Army Hospital the previous month, he had stated that he would not let Iraqi veterans fall through the cracks or suffer unnecessarily. This caused Rev. Graves to wonder about the commitment to Gulf War veterans. Rev Graves hoped that, because of situations like Walter Reed, the issue of Gulf War veterans' illnesses also might be elevated into the public consciousness.

Mr. Hardie commented that Dr. Steele's presentations had been fabulous. The most compelling point that he had taken from them was that it was within scientific reach to identify diagnoses and treatments for ill Gulf War veterans. He thought this was implicit in the draft report. He also noted that comments had been made in a recent Congressional committee meeting suggesting there might be Homeland Security issues surrounding this issue. There are issues beyond Gulf War veterans, and Mr. Hardie noted that the pledge had been made by many that it would never happen again. He acknowledged Dr. Bloom's point that some will take this report and pick it apart. These concerns needed to be addressed while also speaking at a lay level.

Dr. Steele agreed that the report needed to speak at both lay and scientific levels. The challenge of compiling this report had been to be as comprehensive and sharp as possible in the scientific presentations in order to address controversies in the scientific community, while also speaking in plain English.

Chairman Binns thanked everyone for the day's discussion.

Public Comment – Day 1

Ms Angela Newbold, whose son is a veteran from the first Gulf War, spoke to the Committee. Ms. Newbold was from Omaha, Nebraska. She stated that before listening to the Committee's discussion that she had never heard from civilian or VA physicians that this problem existed. If anything, her son has been told over and over that the paperwork wasn't worth his frustration. Ms. Newbold stated that her son had served in a Marine helicopter unit that was at Al Jubayl during the reported SCUD attack in January 1991. She discussed her son's health issues which began immediately upon his return, including difficulty in breathing, temperature and light sensitivities, depression, psychosis, fatigue, cognitive difficulties, etc. He was diagnosed with multiple sclerosis (MS) earlier this year, but has not received treatment. He is now unemployed with four young children. Ms. Newbold stated that the word needed to get out to the physicians that this was a problem. It was difficult for the ill veteran to fill out the paperwork and there are hurdles for family and others to help them in this process. These veterans need help. She stated that she would be the feet for these guys and help get the word out. She was thankful for what the Committee had shared and was doing to help.

Chairman Binns and the Committee thanked Ms. Newbold for her comments.

Ms. Denise Nichols, a Gulf War veteran, spoke to the Committee. She stated that she had spent the previous day at the Capitol. She said that there was a lot of work that needs to be done, and that the work of the Committee was great. She agreed that the report needed to be written so that a lay person could understand it. She commented that one of the Congressional staffers that she had spoken with the previous day had written a report on Gulf War illnesses back in 1994-1995. The staffer had asked her whether more was now known. She stated it was like starting the process again on the Hill. There was a new political party in control of Congress, one that had not been control in eight years. They are regaining their footing. She is working to convince them that work still needs to be done on this issue. This doesn't help with transitions, especially ones that are being made in the scientific world. This doesn't help the Committee or veterans get across the point about this problem. She stated that it needed to be addressed in the media, e.g., letters to the editors. She noted that it had been sixteen years since the war, and a lot of work was still needed on the Hill and with the press. She was not as optimistic as the Committee. She stated that the situation at Walter Reed Army Hospital had taken three to four years to be exposed. And while it had been exposed, we aren't getting to the "meat" of the issue. We are lucky to have mothers and wives who will stand by ill Gulf War veterans upon their return. And their stories need to be heard by the public. She asked that the Committee put pressure on the VA to release information and statistics about veterans' cancer and immune diagnoses. This information should be shared as readily as the Gulf War Veterans' Information System (GWVIS) data. She believed that the autoimmune disorders may also have increased, in parallel with oxidative stress. Gulf War illness may be a prediagnostic stage of diseases that develop later such as ALS or Parkinson's' disease. Ms. Nichols gave the Committee information about Operation Iraqi Freedom (OIF) and Operation Enduring Freedom (OEF) veterans' rates of chronic multisymptom illnesses. She stated that sampling and surveys of these veterans needed to be done. Ms. Nichols stated that she had recently served on a panel reviewing proposed research and was shocked by the cost of research. She had conflicting feelings because veterans were still waiting, with many still being sent to psychological units. She stated that the system was broken and it needed to be addressed. She stated that she has put out a petition to support more DoD Gulf War illnesses research funding. She indicated that 450 individuals had signed the petition. She asked that the Committee members help Gulf War veterans get this issue back in view. Without this attention, things don't get done on the Hill.

Chairman Binns thanked Ms. Nichols. He asked if there were any additional comments from the public or Committee. Dr. Meggs stated that what the Committee just heard emphasized the importance of longitudinal studies, e.g., what has happened to these veterans since 1992-1996. Questions about if more veterans have developed neurodegenerative diseases need to be addressed and should be a priority.

Chairman Binns thanked everyone again. The meeting recessed for the day at 4:58 p.m.

Day 2

The meeting reconvened on Thursday, April 25, 2007, at 8:37 a.m. in Room 230, VA Headquarters, 810 Vermont, N.W., Washington, DC. Dr. Barlow was not present for the second day of the meeting.

Committee discussion: 2007 RAC-GWVI report – Day 2

Dr. Steele resumed the discussion of the Committee's draft 2007 report. (See Appendix – Presentation 5.) She reviewed the approach that was used throughout the report, and noted that the largest section would deal with etiologic factors for Gulf War illness, since this had been a major focus of the Committee meetings.

During the discussion of recommendations in Section 1 of the report, Chairman Binns wondered if it might be appropriate to add "behavioral" to the types of problems studied in the children of Gulf War veterans. Dr. Steele stated that VA had conducted a survey of Gulf War spouses and children. However, the data and results with respect to the children had not been published. From preliminary drafts that she has seen, it appears they are focusing on psychological versus behavioral problems. Chairman Binns asked if Dr. Steele could incorporate this preliminary information in the report. Dr. Steele stated that, in its 2004 report, the Committee had called upon the researchers to publish their results and that this would could be reiterated. She indicated that she could speak to the researchers to see what their progress was in this area.

Members discussed the issue of whether the Committee should recommend a specific Gulf War illness case definition. Dr. Steele said that the CDC chronic multisymptom illness case definition that had been used by several Gulf War illness research projects had not really served the research well, since the case definition is highly nonspecific. She stated that previous Committee recommendations had been limited to directing the need for using well-constructed and clearly-described case definitions. She asked for comments from the Committee on this issue.

Dr. Clauw stated that the old definition of chronic multisymptom illness was particularly terrible in light of the Committee's focus on treatments. One treats certain domains of symptoms with certain classes of drugs and types of treatments. If someone has a lot of pain, there are certain drugs that will work for the pain, but won't work for the other symptoms. These individuals might not meet the definition of chronic multisymptom illness. But it is even more problematic when people who do meet the definition are placed in a drug trial, and any effect is diluted. Dr. Clauw stated that the Committee should encourage researchers to be diligent in defining cases, but thought it would be a bad idea for the Committee to be too proscriptive in this regard. This condition doesn't look the same in all people, and everyone should not be treated the same. His team has focused on treatments for chronic widespread pain, but it was naïve to think we will find a single treatment to treat all of these individuals. He stated that this was the problem with the treatment studies in late 1990s, i.e., too broad of a case definition with a finding that nothing worked.

Dr. Golomb agreed and stated that until the pathophysiology was understood, it was likely that any case definition would include some of the right, as well as wrong, individuals. There is utility in having different case definitions to see emerging patterns and results so long as they are clearly described.

Dr. Steele understood the points made by Drs. Clauw and Golomb, but thought there were downsides to not establishing a single case definition. It made results obtained by different studies difficult to compare, and made it difficult to obtain a real prevalence figure. She thought that, in light of the disagreement on this issue, the Committee's current proposed recommendation was a middle ground, that is, the recommendation that investigators use a well-described and justified case definition.

Dr. Meggs stated that there could be a case definition, but it shouldn't be one that excludes anybody who doesn't have chronic pain, memory problems, etc. The case definition must relate to the exposure and illness in some way to include all the subgroups. And, as Dr. Clauw noted, one has to be careful once they begin looking at treatments.

Dr. Steele stated that when she was putting together the case definition for the Kansas study, it was not too difficult to identify a pattern of symptoms that distinguished deployed Gulf War Veterans from nondeployed veterans. It seemed to her that the best case definition would be an umbrella definition with identifiable subgroups, e.g., Gulf War illness with chronic widespread pain, Gulf War illness with chronic

gastrointestinal problems, etc. This would be a case definition that distinguished Gulf War veterans with excess symptoms from more healthy individuals, and then identifies specific subgroups of interest for specific studies. She believed that there was a way to develop a good case definition, but that it had not been done. Ultimately, this had impeded progress.

Dr. Nettleman stated that she didn't think the field advanced politically without a having a case definition. She stated it was a difficult thing to do. Other chronic multisymptom conditions had "hung their hat" on a definition. She understood the concern to not have it too vague or too specific, but thought it was important to have for the advancement of the field.

Dr. Clauw stated that there was a lot of precedent for having different types of case definitions in different types of studies. All he was saying was that as the suggestion was being made to move into the treatment realm, making any type of case definition recommendation would be a problem. Dr. Steele asked Dr. Clauw if his currently proposed chronic widespread treatment research projects were focused on individuals with widespread pain or more generally on Gulf War veterans with diverse symptoms. Dr. Clauw stated that most people with chronic widespread pain also have the other somatic issues, e.g., fatigue, insomnia. But most have pain and this should be the primary outcome measure in clinical trials of treatments that address pain. This was the problem with the late-1990s clinical studies, in which the primary outcome measure was too diffuse, and a shot-gun approach to treatments was used. Even if they had used the right treatment for some veterans, the studies were flawed.

Chairman Binns said he recalled Dr. Clauw's mention of this point at the November 2006 Committee meeting, as well as his support for using the Kansas case definition. Chairman Binns noted that many new researchers coming into this field may not be aware of the complexities surrounding this issue. He wondered if there might be a way to give a "backup definition" so that someone who is not expert would have a sense of how to define Gulf War illnesses and not go off and pick an irrelevant definition.

Dr. Golomb thought this was an interesting point. She thought that one of the best definitions available was the Kansas definition, because it provided better discrimination. She wasn't sure if the CDC case definition might have slightly greater sensitivity. It might be worth saying that definitions that have been used include "blank" and "blank", with "blank" providing better discrimination between deployed and nondeployed, and barring some strong reason for selecting another definition, "blank" might be the preferred definition. She thought there were situations for having a different definition. Dr. Steele stated that it was hard to justify which single definition should be used, but by default everyone goes to the CDC chronic multisymptom illness definition, which hasn't served well. Dr. Golomb added that she believed that the final definition would have to be driven by a better understanding of the mechanisms of the illness. Dr. Steele stated that she agreed with Dr. Nettleman's point that once chronic fatigue syndrome and fibromyalgia were defined in some way, things started moving forward.

Dr. Meggs stated that the Committee had to be careful about the case definition. This argument comes up over and over again and can be used as a smokescreen to avoid the main issues. He related a situation at a MCS conference where an individual stated that they couldn't study it because there was no case definition. However, there were twelve case definitions and the issue was which one should be used. A case definition is never going to represent absolute reality and is needed for cloudy situations. As the field evolves, the case definitions will be refined. There is no perfect case definition, and individuals should not get hung up on it. Researchers need to state what they are going to study, what their inclusion and exclusion criteria are, and how their results apply to individuals who fit this definition. This is all there is to it.

Dr. O'Callaghan stated that he agreed with Dr. Meggs. He referred to an analogous situation associated with defining neurotoxicity. He remembered thinking that it had been too broad, but it brought the parties to the table and as the field matures, one begins to pick and chose the best definitions to move the field forward on a scientific basis.

Dr. Golomb noted that even in well-studied areas such as heart disease, there was no specific case definition for all studies. And despite this, the field has moved forward.

Chairman Binns noted that there were two case definitions between which most researchers picked: the CDC and Kansas definitions. People who didn't know any "better" pick the CDC definition, while everybody sitting around the Committee table think it is a "bad" definition. He wondered if a researcher should be advised to use the Kansas definition, if there wasn't a reason to choose a more narrow definition. However, the real question was what definition would the Committee like Dr. Robert Haley and his colleagues or DoD-funded researchers to use. From a logical and pragmatic point of view, if the Committee liked the Kansas definition over the CDC definition, this needed to be said.

Dr. Clauw agreed, but thought the Committee needed to be careful as to how it is worded. He thought it could be said that the Kansas definition had performed better in many ways than the CDC definition, and that for future epidemiological and perhaps treatment studies, this would be the preferable definition. However, researchers should not be locked into using it. He noted that when he went to write grant proposals for his own treatment studies, it was difficult to use the Kansas definition because it would include too many people that he didn't think would respond to the particular intervention.

Dr. Meggs stated that one could use the modified Kansas definition for one's particular end point. However, every study is different. It was like choosing a p value.

Dr. Steele stated that she appreciated that everyone liked the Kansas definition. However, while she had validated it in several studies, she hadn't had time to publish the results of the validation studies, so was not comfortable making this particular recommendation at this time.

Dr. Melling commented that that the problem was how one described someone as suffering from Gulf War illness. Essentially it is a combination of multiple symptoms and that they had served in the Gulf War. Having defined someone as suffering from Gulf War illness, one really needs to use a narrower definition of primary symptoms to evaluate treatments. This is because they are not going to be the same for all Gulf War illnesses. In evaluating a particular treatment regime, one focuses on the symptoms presented. The two positions are entirely consistent. Dr. Melling thought it would be good if this could be spelled out in the report.

Dr. Steele thought this would be a very Solomonic way to handle this. She stated that wording reflecting these suggestions would be drafted for further Committee review.

With respect to other issues associated with epidemiologic studies, Dr. Nettleman suggested it be noted that corrections for multiple comparisons were sometimes not made in earlier studies and were needed.

With respect to the discussion of research of psychological stressors in Gulf War veterans, Chairman Binns noted that as of 2003, 57% of all Gulf War research was going towards research on stress. He stated that it wasn't as if this area hadn't been thoroughly researched. Thus, the Committee recommended in 2004 that additional research into this area was not needed.

Dr. Golomb stated that she wondered if it should be more strongly worded, because she worried that some of the research funded after this recommendation that had been identified as relating to "neurotoxic exposures" or "PB and stress" were really focused on stress. She wondered if researchers would use the wiggle room to continue researching stress as the primary factor.

Dr. Steele stated that right after the 2004 report, there was still a high level of stress-related studies being proposed. However, when the VA 2005 funding announcement came out, the number of stress-related proposals had dropped significantly.

Dr. Melling wondered if it might be helpful to recognize that PTSD was an issue after conflicts, and that nobody questioned this. However, this is not what is being studied in this issue. This is illness over and above that which could be explained by stress. It is legitimate to look at stress, but not in the context of Gulf War illnesses. Dr. Golomb agreed that this was worthwhile point that needed to be made.

During the discussion of oil well fire exposures, Dr. Meggs commented that virtually 100% of the patients that he has seen with chronic asthma that developed after high-level respiratory exposure also have multisymptom illness. This is an important point, and begs the point that patients with multisymptom illnesses have objective diagnosable medical conditions, like asthma and rhinosinusitis, that aren't being recognized. This is lost sometimes in this whole argument. Just because an individual developed asthma from the oil well fires doesn't mean they might not also have chronic headaches, mood disorders, myalgias, etc. Just as their asthma can be exacerbated by subsequent exposures, these other symptoms can too.

Dr. Steele stated that there were several studies looking at pulmonary function in Gulf War veterans, but they always look at deployed versus nondeployed. There have not been studies that looked specifically at pulmonary function in relation to oil well fire exposure.

Mr. Hardie commented that he had researched the literature on particulates and oil well fires about a decade ago because of his own symptoms. He stated that he did not believe that his exposure to oil well fires was the sole cause of his health problems, but that there was a direct correlation with his respiratory problems. He has been diagnosed and undiagnosed with asthma and chronic sinusitis and concurred with Dr. Meggs' point. He asked if information from the Agency for Toxic Substances and Disease Registry (ATSDR) information about particulates, especially ultrafine particulate exposure, could be incorporated into the report. Dr. Steele stated that this information was present in both the oil well fire and particulate matter sections of the report. She said that the ultrafine particulate studies described related more specifically to neurological function as a result of ultrafine particulate inhalation. These studies had been conducted in animals. She was not aware of the respiratory effects of ultrafine particulate exposure. Mr. Hardie stated that what he found interesting in his reading was that there were exposures that exceed 80 times or more the published acceptable rates, even months after the oil well fires. Dr. Steele agreed that particulate exposures in this region are heightened and oil well fires just contributed to the problem. She noted that rates of asthma were also higher in this part of the world. She stated that measurements taken during the Gulf War indicated that 25% of the airborne particulates came from oil well fires, while 75% was attributable to background levels. Mr. Hardie said that he just wanted to make sure that this report did not replicate his concerns with DoD's previous reports and diminished concerns about particulate matter. Dr. Steele stated that the report does recognize this issue, but it was difficult to identify specific research recommendations. Mr. Hardie replied that he wasn't sure if more research was needed on particulate exposure, just that the already identified results of such exposure should be addressed.

Dr. Clauw commented that, in general, the Committee should be thinking in this way. An example would be sarin. No one would say exposure to sarin is good, but there is a point at which we must "move on."

Because of limited funds, the only exposures, in his opinion, that should be focused on are the exposures to which future troops may experience. Dr. Steele thought it was important that Gulf War-specific exposures should be studied so that a better understanding of the pathophysiology of Gulf War illness could be obtained. For example, this might prevent future troops from being given PB. Dr. Clauw stated that he agreed with research into PB. However, he stated that few would say exposure to sarin would be a good idea. The goal will always be to prevent our troops from being exposed to sarin. When there are limited monies, recommendations need to prioritize. He did not believe that equal weight should be given to studies on sarin and PB. Dr. Steele noted that in her discussions with Gulf War researchers, some have commented that research on effects of low-level cholinergic agents, in general, will unravel the mysteries of Gulf War illness. While some may not agree that low-level sarin exposure is the cause, this type of research may still be helpful. Dr. Clauw stated that the Committee, however, had a duty to prioritize their recommendations. Other than stress, the Committee isn't discouraging research into the other exposures. Dr. Steele commented that many people at the table would disagree with Dr. Clauw about the importance of sarin research. Dr. Clauw acknowledged this. However, he was suggesting that the same standards be applied to all areas of research, regardless of individual members' feelings.

Chairman Binns stated that there was a tendency for a committee like this to fine-tune everybody's research and imagine all the research that could be done. However, this was not consistent with limited resources. Just as Mr. Hardie noted, particulate matter research was important but it has been done and won't help make anybody healthier. Mr. Hardie commented that he appreciated the need to track various diseases and suggested adding respiratory diseases to this list. This would help to confirm what the ATSDR findings on particulate matter. Chairman Binns noted that this was something that could be done in one study, such as Dr. Kang's longitudinal study. An additional $5 million study would not be necessary.

Dr. Melling stated that another recommendation criterion to be considered is how the particular research relates to potential treatment. If a study with respect to neurotoxic agents may relate to treatments, this would raise its priority. Dr. Golomb agreed and commented that it would help better define mechanisms and lead to treatments. She noted that she would not prioritize sarin research as high as Dr. Haley might though.

Rev. Graves commented that it "sucks" being a Gulf War veteran in a VA hospital right now. For this reason, he is no longer seeking care through the VA system. His problem is that he comes in with certain symptoms, but his primary diagnosis is PTSD. The VA physicians just don't get it. When the Committee discusses what it is going to do and issues like case definitions, it also needs to make clear that troops had very specific exposures. If this is not done, many of the physicians will continue to believe it is all "mental." Rev. Graves stated that he knew that he was exposed to sarin and other toxic agents. However, his physician ignores this and makes the diagnosis of PTSD. There needs to be "power" behind this point. Without a case definition of Gulf War illness and the statement that it is important, the rest of this was meaningless. The message was not getting out there. Dr. Steele stated that, from a research perspective, this was a great argument for a case definition. But more importantly, Rev. Graves' point goes back to the earlier discussion that the central point of the report is that Gulf War veterans are ill as a result of their service in the War, that it is not PTSD or other psychological condition, and it is a serious problem. She said it was important that this be conveyed clearly.

Dr. Clauw agreed with the points made by Rev. Graves, and noted that to date almost all of the Gulf War illness research monies had been spent looking at the cause. Almost none has been spent on treatment. When a veteran goes to their physician, the physician does not know what to do for him or her. The one thing that they do know how to treat is PTSD. They don't know what to do for a veteran's pain, fatigue, memory problems, etc.., because treatment studies haven't been done in this area. Three drugs are about

to be approved specifically for fibromyalgia, which will finally give physicians something to prescribe for these patients. Dr. Clauw stated that he was suggesting that the focus of the limited research funds should be placed on treatments. Rev. Graves agreed, but noted that there was huge educational gap between ongoing research and the clinical field. Dr. Steele stated that she had also often heard from veterans of the problem that Rev. Graves was raising.

Dr. Meggs said that part of the problem was the limited charge of the Committee. It is not the charge of the Committee to change the attitudes of the VA physicians. The most that the Committee can do is point the way to research that will someday do this. Dr. Golomb commented that the publicity surrounding the release of the report would itself educate the physicians. Chairman Binns acknowledged that the Committee was limited to research, but that the Committee had, in the past, recommended the revision of clinical guidelines to be in line with current research. He stated that this could go into the report. Many members agreed. Dr. Golomb agreed with Dr. Clauw's point that giving physicians better tools will empower them to do something. However, better education of physicians is important too. Many of the VA physicians that she works with remember their training from a decade ago that implied that Gulf War veterans really aren't ill and if they are, it is all "in their head." Some of these physicians will refer Gulf War veterans for a single clinic visit, and the veteran ends up asking for a transfer to her clinic. Just having a physician who believes their complaints are real and takes their suffering seriously makes a big difference to these veterans. Dr. Steele stated that this could be discussed in the report's narrative. Dr. Meggs noted that a book had recently been published on how physicians think, analyzing the attitudes of American physicians. This book notes the same problems that Rev. Graves raised, and the problem goes beyond the VA healthcare system.

Dr. Steele asked members to forward any additional comments on these issues to her for incorporation into the report.

Mr. Hardie reiterated his suggestion that monitoring of respiratory disease be included in the recommendations of this particular section. With respect to epidemiological studies, Dr. Steele commented that it appeared the consensus was to add this. Rev. Graves noted that this should cover both upper and lower respiratory diseases. Dr. Steele asked for clarification of whether this was with respect to the subset of veterans exposed to oil well fires. Mr. Hardie agreed that it was.

During the review of the specific subgroups that needed to be studied with respect to depleted uranium exposure, Rev. Graves noted that during the ground war, forward deployed troops drove through smoke from burning tanks hit by depleted uranium munitions. He stated that all of the combat troops were driving through this smoke. Dr. Steele agreed that there were veterans who were exposed in this manner, and that another subgroup went in after the battle and handled the contaminated tanks. However, for research purposes, these individuals were harder to identify and any idea of the extent of their exposure was difficult to ascertain. With the Camp Doha subgroup, researchers could identify troops' presence on a specific date at a specific location to a specific exposure. This particular recommendation was intended to make the study "doable."

Dr. O'Callaghan commented that this might be one of the cases where the animal studies have gotten ahead of epidemiological studies. Dr. Steele agreed. However, the Committee had earlier concluded that while the animal studies were intriguing and important and should be continued for learning about depleted uranium effects in general, it was still not known whether depleted uranium is specifically related to Gulf War illness. As a result, the Committee had agreed at a previous meeting to recommend epidemiologic evaluation of this question, before making specific recommendations for animal studies looking at effects of depleted uranium exposure.

Dr. Golomb said that the draft recommendation to study the identified DU exposed cohorts, along with all of their diagnosable medical and psychiatric conditions, was a huge, involved, expensive proposal. She wondered if the first step would be a survey that identifies exposure levels better within an existing epidemiological study. Dr. Steele summarized the rationale for the DU epidemiologic proposal, saying that a number of outcomes had not been reported from previous studies, including multisymptom illness and two tumors in the small Baltimore DU cohort, and no findings on reproductive outcomes in relation to DU. She indicated that the tests recommended in the draft just reflected what was already being done in the Baltimore study, but perhaps there could be an initial survey to get self-reported symptoms, cancers, etc., to provide an initial indicator of the extent of the problem. Dr. Golomb thought this was great and wanted to be careful that excessive funding not be used for the study without a better idea of whether DU had played a role in Gulf War illness. Chairman Binns also liked this suggestion, i.e., that this recommendation was in the "important" but not "priority" level. It also has the Committee going on record about this issue, which it should. Dr. Steele stated that she believed Dr. Haley's epidemiologic study had a way to track the Camp Doha group.

Mr. Hardie suggested the inclusion of "inhalation and/or ingestion" of DU be assessed in relation to friendly fire incidents. Otherwise, some researchers might not recognize this particular mode of exposure, assuming exposure was limited to shrapnel wounds. He stressed that Gulf War veterans had pledged many years ago that future generations should never again be exposed to things Gulf War veterans were. He noted that 600,000 pounds of depleted uranium was still littering the Iraqi desert, continuing to expose anyone there. He thought it was disappointing that more research hadn't been done to better understand the health effects of depleted uranium, separate from the concerns of Gulf War veterans' health. He noted that there were safety training measures for depleted uranium that were barely used. While this may not be a priority for the chronic multisymptom illness being discussed, he hoped that it could convey the need to monitor this issue for at least the life of Gulf War veterans.

Mr. Atizado noted that the DoD had recently released the Capstone Report, which essentially closed the door on this issue for them. Dr. Steele noted that it was an amazing project, but their focus was not on Gulf War illnesses. It didn't really answer the questions that are before the Committee. Mr. Atizado agreed and stated that he had personally heard quite a bit of criticism of this particular study.

Dr. Meggs wondered if mention should be made about the latency periods for cancer and that these studies needed to be continued for the lifetime of Gulf War veterans. Dr. Steele stated that she thought this should be made clear in the first section about cancer studies in general. She wondered, however, if wording should be added that this monitoring should be done at regular intervals.

Before moving into the discussion related to vaccines, Chairman Binns interrupted and suggested holding further discussion of the report until later in the day. He noted the need to keep to the scheduled agenda and the presence of the next scheduled speaker.

The meeting recessed for a break at 10:04 a.m.

The meeting reconvened at 10:25 a.m.

VA Office of Research and Development Update on Gulf War Illness-related Research Activities

Joel Kupersmith, MD, VA Chief Research and Development Officer
William J. Goldberg, PhD, VA ORD Gulf War Research Portfolio Manager

Dr. Joel Kupersmith, VA's Chief Research and Development Officer (CRADO) stated that he didn't have a report to share about the ongoing discussions involving Dr. Robert Haley's research program at UTSW. However, they were looking forward to getting several projects started there. Dr. Kupersmith noted that the most significant issue that VA's Office of Research and Development (ORD) had been addressing lately involved the security of its information technology. He thought they had made considerable headway on this issue and looked forward to VA being a leader in this area.

Chairman Binns stated that he had heard from Dr. Haley the previous evening. Dr. Haley had shared that contract discussions were going well. Several issues had been addressed and "all systems were a go" for the program.

Mr. Hardie thanked Dr. Kupersmith for the continuation of the Gulf War Veterans' Information System (GWVIS) reports, and asked if he knew when VA's next geographic distribution of expenditures report would be released. Dr. Kupersmith indicated that he did not, and that this report was prepared by a different office within VA. Mr. Hardie noted the Committee's earlier discussion about tracking cancers and other medical conditions in Gulf War veterans. He wondered if there was something that VA could already be doing about this before the official Committee recommendation would be submitted. He thought that this would be very helpful.

Chairman Binns noted the Committee's discussion about the need to educate VA clinicians regarding the latest research. He noted that they were essentially operating out of a manual that advises them to treat these conditions as psychological in nature. While the Committee's charge is not to get into clinical issues, he noted that the Committee had recommended that the guidelines be revised to reflect the latest research. He wondered if there had been any efforts made in this regard. Dr. Kupersmith was not sure, but indicated that they could convey the information to the Secretary. He stated that there were a number of programs within ORD, such as translational research, that related to clinical care. However, ORD doesn't have control over VA's clinical programs. Chairman Binns noted that the Committee had discussed the recommendation at its August 2006 meeting and that it had already been conveyed to the Secretary.

Dr. Meggs asked whether the appropriations for Dr. Haley's program were separate from other funding, i.e., if the UTSW funding would impact the funding available for other investigators. Dr. Kupersmith stated that it was separate but part of the ORD's total budget.

Dr. Golomb noted that the mandatory physician Gulf War illness training in 1997-1998 contained a number of principles that were directly contrary to the findings of the Committee. Because physicians are still operating under these wrong ideas, she felt it wasn't in the best interest of veterans to remain under care of clinicians with this set of beliefs and training. Dr. Kupersmith understood and indicated that the best that ORD could do was convey these concerns.

Chairman Binns asked Mrs. Newbold if she would share her concerns about VA clinical care for Gulf War veterans with Dr. Kupersmith. Mrs. Newbold explained the health concerns that her son has faced over the past ten years, falling though the cracks of the system with no follow-up care. She stated that she was thankful to hear the discussion of the Committee, but was concern about keeping the clinicians aware of the research. She wondered whether this was being communicated to them, and indicated that it was frustrating for the veteran and their families. They ultimately will just stop coming to the VA. She stated

that something needed to be done to address this. Dr. Kupersmith thanked Mrs. Newbold for her comments. He offered to discuss her son's case with the clinicians to help improve his care.

Ms. Nichols requested that VA ORD communicate with researchers across the country as well, not only within VA but within DoD too, about this field of research. She suggested that VA ORD go to the various national medical meetings and spread information about this issue. A poster presentation could help in this regard. Dr. Kupersmith stated that VA ORD encouraged its investigators to present their research at these meetings. He didn't have a record of the various areas, but reiterated that this was strongly encouraged. As for DoD, he could not speak to their researchers' activities. Ms. Nichols noted that this had been discussed by one of DoD's Congressionally Directed Medical Research Program (CDMRP) panels. The priority research studies needed to be targeted, and this information should be disseminated. Dr. Kupersmith agreed that it was beneficial to all to have the researchers present at these meetings. He did note, however, that not all presentations or abstracts are accepted at these meetings. Chairman Binns noted that the American Academy of Neurology had selected a VA poster presentation by Dr. Roberta White to highlight at its meeting the following week. Dr. Kupersmith stated that poster presentations were good vehicles for conveying information because the investigators speak individually with the other researchers. This exchange does encourage more research. Ms. Nichols suggested that this particular poster presentation be included in the VA research update, which Dr. Kupersmith indicated would be reviewed.

Dr. William Goldberg gave an update on the status of VA's Gulf War illness research portfolio. (See Appendix – Presentation 6.)

During the discussion of the FY2006 Gulf War portfolio, Dr. Golomb inquired about the inclusion of research into a vaccine for leishmaniasis being included in the Gulf War portfolio. Dr. Goldberg stated that one of the issues of concern listed for Gulf War veterans was leishmaniasis. However, they are in process of doing a new portfolio analysis. He stated that it was likely that several projects would no longer be listed as part of this portfolio, with most of the current leishmaniasis research being moved to the OIF/OEF portfolio. These projects won't be "cut-off", but there particular area of relevance will be modified.

Dr. Steele commented that the total list of projects being shared by Dr. Goldberg were from 2006. She noted that previously lists had been reviewed by Committee staff to identify whether the project focused on (1) Gulf War illnesses or exposures, (2) other issues related to Gulf War service, or (3) was only marginally related or not related to Gulf War service. She noted that the portfolio currently contained some leishmaniasis projects that had nothing to do with Gulf War, and some were potentially related to the Gulf War. Overall, projects identified for inclusion in the "Gulf War" research portfolio may not be the same as projects considered Gulf War research by the Committee. Dr. Steele stated that approximately one third of the portfolio funding was for ALS research, most of which was not related to Gulf War veterans.

Chairman Binns noted that the Committee had raised this concern previously. He was glad to hear that Dr. Goldberg was addressing it with his review of the portfolio project classifications.

Dr. Goldberg stated that when classifications were made by ORD, they were used for multiple purposes. He acknowledged the objections to the amount of ALS research counted towards the Gulf War portfolio, but noted that there was more ALS research that was not included in this particular portfolio. He acknowledged that ORD definitions may not always match the definitions of the Committee, but that they take the Committee's viewpoint into consideration when reanalyzing the portfolio.

Mr. Hardie noted the concern of ORD's classification of one-third of the Gulf War portfolio monies towards ALS research when roughly 175 Gulf War veterans suffer from this particular disease. Dr. Goldberg stated that Mr. Hardie's question would make sense if the VA research program was service-directed. However, VA's research program is investigator-directed. If ALS, particularly treatment of the disease, is of concern to Gulf War veterans, it is a potential area of research that needs to be considered for inclusion in the portfolio. This is because these are the proposals submitted by VA investigators and are the ones selected for funding. When they select projects, they don't say "this isn't chronic multisymptom illness, so we can't fund it." If it is relevant, they will include it.

Mr. Hardie stated that since there is evidence of elevated rates of ALS and MS for veterans of all eras, how can: (1) the funding be changed so that it is not associated with this particular portfolio; and (2) the funding be changed so that the vast majority of the research dollars benefit the vast majority of ill Gulf War veterans. Dr. Goldberg stated that he could remove all of the listed ALS projects from the Gulf War portfolio, but it wouldn't stop the VA from funding these projects. Mr. Hardie stated that this was not what he was suggesting. Dr. Goldberg stated that ORD included them because the projects are relevant to diseases that may affect Gulf War veterans, and their focus is not just chronic multisymptom illness. He noted that the Committee itself seemed to vacillate on this point during its discussion earlier in the morning. Dr. Steele clarified that the discussion had focused on Gulf War-specific research in the different areas discussed. Dr. Goldberg noted that he could remove all of the projects in question, and there would then be a smaller amount of money identified for Gulf War research. However, this did not mean the studies would be replaced with any new projects. If this would make the Committee happy, ORD could do this.

Mr. Hardie noted that these numbers have a "life" outside of VA, particularly on Capitol Hill. When Congress is not getting a clear picture of the number of Gulf War illness-specific research projects being funded, it is an injustice to the ill veterans. Congress now sees numbers that suggest that a lot of money is being spent on studies, but these may not be studies specific to Gulf War veterans. Mr. Hardie indicated that he wasn't saying that ALS, MS, MS-like symptoms, etc, were not a problem for Gulf War veterans, but not just specifically to Gulf War veterans. Congress should be given a more realistic picture of what is being funded. Dr. Goldberg expressed concern that removal of these projects from the portfolio would indicate that VA, as a research entity, did not consider ALS research an important issue within this realm. The inclusion of this research in the portfolio is a reflection of VA's position that ALS is an important disease as it affects Gulf War veterans.

Dr. Golomb asked if this meant that Gulf War veterans who have MS could be service connected. Dr. Goldberg responded that research did not determine service connection. Whether there would be a service-connection is a benefits issue. This has nothing to do with research areas that VA, as a research organization, determines are priority areas. Dr. Golomb stated that the point that she was trying to get to was that she thought ALS and MS were important issues, but was concerned if all Gulf War research monies were directed towards this type of research none would be directed towards the chronic multisymptom illnesses. The vast majority of Gulf War veterans are not suffering from ALS. Thus, the proportionality should be considered in allocating the budget.

Chairman Binns stated that it seemed clear that the Committee, in general, would like to see the portfolio reflect the actual studies that are specifically directed at Gulf War veterans. Some of the ALS studies are specific in this regard, but many are not. While this would reduce the portfolio numbers, this seemed to be the consensus around the Committee table.

Dr. Clauw stated that it seemed likely that the majority, if not all, of the money spent by VA on Gulf War research in the next year or so would be going to UTSW. Given this, he asked whether anyone within

ORD or the Committee would be asking Dr. Haley to align his priorities with the priorities that will be laid out in the Committee's report. Dr. Goldberg stated that this was not part of the contract with UTSW as far as he knew. Dr. Steele said that the report would advise on all federal Gulf War research funding. This would include CDMRP funding, not just VA funding. She added that it wasn't clear initially if there would be more VA Gulf War RFAs (requests for applications).

Chairman Binns noted that this was the "Research Advisory Committee." The Committee has never had any authority other than to give advice. If the program at UTSW would be getting a lion's share of the VA Gulf War funding, the Committee had an obligation to subject it to the same review process and recommendations as if it were being run by VA ORD itself. He noted that he was pleased that VA ORD continued to accept Gulf War proposals under VA's standing funding mechanisms. However, the Committee has never depended on anything other than the authority of the science to persuade individuals to do as the Committee recommended. Dr. Haley has an interest in having his program being well regarded within VA, the scientific community and Capitol Hill. If the Committee finds that he is doing a good job, this will reflect well on him. If not, it may reflect that changes need to be made. The Committee will treat the UTSW program just as it would any other VA research program.

Dr. Steele asked if Dr. Goldberg had a sense about whether Gulf War proposals were coming in from the field even though there is no specific Gulf War RFA. Dr. Goldberg stated that there was one in the current funding cycle. It will be reviewed by the normal merit review committee, with his assurance that ad hoc reviewers would be added to ensure appropriate review. There would not be a special Gulf War merit review committee for this proposal.

Dr. Golomb asked for clarification about whose research the Committee would now be advising on. Chairman Binns stated that the Committee was not just advising on VA research. He noted that the Committee's report discussion had not yet reached the part where the Committee considered what it would recommend that VA continue to do. VA ORD had indicated that there were no plans to continue releasing specific Gulf War illnesses RFAs. The Committee can accept this or recommend otherwise. Dr. Goldberg stated that there were currently no funds in VA's research budget for a specific Gulf War illness RFA.

Dr. Nettleman inquired as to VA's ORD total budget and shortfall. Dr. Goldberg indicated that Dr. Timothy O'Leary could answer this question better than he could.

Dr. Steele inquired about the progress on placing VA research studies onto the Internet, on the clinicaltrials.gov website, so that veterans were more aware of opportunities to participate in research. Dr. Goldberg stated that they were working on this effort. Typically this website is used for true clinical intervention trials, but it is possible to post information on other studies that are enrolling patients for sample collection, etc. It is taking a little more coordination within VA ORD to accomplish than originally thought.

Dr. Steele asked about the status of the ALS registry and Gulf War brain bank. Dr. Goldberg stated that he needed to speak with Dr. Louis Fiore to obtain this report. He knew that they were working on the autopsy protocols. Dr. Steele asked if the ALS registry effort was to be continued, and that she had heard rumors that it would not. Dr. Goldberg stated that it would continue, and that a whole new project was being developed at that time. He said that VA ORD was currently funding two new MS projects, one being an epidemiology study. There are also two clinical MS centers of excellence being funded, one of which is in Baltimore and the other in Portland. The coordinating center is in West Haven, MA. These centers are funded by the clinical care budget. Dr. Steele inquired whether the MS epidemiology study included Gulf War veterans. Dr. Goldberg stated that it did include these veterans and that the research

group had just published a paper that claimed they were establishing a MS registry. He is still trying to get clarification on this because everyone was saying that a registry was not being funded. He noted that the epidemiology study did involve a very large cohort, and it is unclear if there was some confusion related to semantics because of this. Dr. Steele indicated that Committee staff would like to be in touch with the investigators to discuss the need for information about the rate of MS in Gulf War veterans. Dr. Goldberg stated that this particular project was due to start in 2007, but he could not give an actual start date as it was still going through various approvals. He stated that Mitch Wallin in Washington, DC., was overseeing this project. He did not believe Dr. Han Kang was involved with this particular project. Dr. Wallin is affiliated with the Baltimore MS Center of Excellence.

Chairman Binns asked if Dr. Goldberg could provide an update on the progress to revise the VA treatment guidelines and training. Dr. Goldberg stated that these were handled by Dr. Mark Brown's office, and that he had spoken with him about it. Dr. Brown indicated that he was in favor of updating the guidelines but was trying to figure out how to go about doing this. Dr. Brown's recollection was that creating the initial guidelines had been difficult. Dr. Goldberg indicated that Dr. Clauw, who was on this initial panel, could probably attest as to the problems that arose. However, they are interested in doing it. Dr. Goldberg stated that he would be speaking with Dr. Brown and Dr. Kenneth Hyams the next day, and that he would raise this issue with them.

Chairman Binns asked if there was any feedback on the Committee's recommendation of creating an additional public advisory committee to consider Gulf War topics not within the realm of the Committee's charter. Dr. Goldberg stated that he knew that the recommendation was received by the Secretary's office, but was not aware of any response or action. Chairman Binns stated that he would be meeting with Dr. Michael Kussman, VA Under Secretary for Health, on the following day and would raise this issue with him.

Chairman Binns asked whether there was any word on publication of Dr. Kang's longitudinal study. Dr. Goldberg indicated that he would speak with Dr. Kang about progress on this front.

Chairman Binns asked as if there was any word about whether the Gulf War Review would be published in paper and electronically or just issued electronically. Dr. Goldberg believed that the plan was to publish the newsletter in both formats. He stated that he would raise this issue as well with Dr. Brown.

Chairman Binns thanked Dr. Goldberg.

Chairman Binns introduced Col. Janet Harris.

Overview of the Congressionally Directed Medical Research Programs (CDMRP)

Col. Janet Harris, PhD, RN
Director, Department of Defense Congressionally Directed Medical Research Programs

Col. Harris gave an overview of DoD's Congressionally Directed Medical Research Programs, including a status report on the developing FY06 Gulf War Veterans' Illnesses Research Program (GWVIRP). (See Appendix – Presentation 7.)

Dr. Meggs inquired about the short time frame for each stage of the funding process. Col. Harris indicated that part of this had to do with the funding cycle and the time at which Congress actually appointed the funds for the research. She stated that the timing of this appropriation had made things very challenging.

Dr. Steele asked if the time allowed for investigators to submit proposals could be longer the next time. Col. Harris stated that it all depended on when in the fiscal year the monies were appropriated. They can't act until the monies are made available. Not having ongoing funding is one of the challenges of this program. One of the good things about the program, though, is that all studies are funded upfront and the monies are dispersed quarterly.

Mr. Hardie inquired as to why the GWVIRP was not listed on the CDMRP's website yet. Col. Harris indicated this was because it was a one-time funded program. If it does receive more monies, it will be added to the website. Their office is managing several different programs, and they have been scrambling to issue program announcements for the programs they do have. As soon as they have accomplished this, they will go back to post information about this program.

Mr. Hardie asked how much of the $5 million would actually go towards research. Col. Harris indicated that approximately $4.5 million would be distributed. Their management costs run about eight percent. They try to be as efficient as possible because their goal is to put as many dollars into research as they possibly can. All of the programs are required to have an alternate list of projects to be funded so when there are management cost-savings, these monies can be rolled over and funding provided for more projects.

Chairman Binns thanked Col. Harris for the presentation and the other CDMRP individuals in the room who had contributed to making this program a first step in solving some of the treatment questions and needs of Gulf War veterans.

Rev. Graves asked whether it was possible to have a category on the CDMRP website for Gulf War illness. Col. Harris said it that it was and that they would work on doing this. She indicated that they had a very good search engine, and if one enters "Gulf War illness," it will pull up all the studies that they have funded. While this is the first time they have had dedicated monies for Gulf War illness, they do have another program that has funded some Gulf War studies in the past. She noted that these studies inadvertently had not been included in the VA report because VA was not aware of their portfolio.

Chairman Binns noted that the Committee's 2004 report not only recommended funding for VA, but also for DoD. This particular program has proved in its first year to correct for a number of the frustrations with previous Gulf War illness funding programs. While the programmatic effort is not yet final, he and many in the audience have tried to convey to Congress that it has been effective and should be continued to be funded at the levels recommended in the Committee's 2004 report. After four years of not having anything good to say, he was glad to finally be able to report good programs were being developed at VA and DoD and resources should be put behind them.

The meeting recessed for a break at 11:39 a.m.

The meeting reconvened at 11:50 a.m.

Committee discussion: 2007 RAC-GWVI report – Day 2 (cont.)

The Committee resumed discussion of the draft 2007 report. (See Appendix – Presentation 5.)

During discussion of the vaccine section, Dr. Steele reported that Dr. Alving had shared that the lab analyses in their DoD squalene study have been completed, and they were currently working on the

statistical analyses. Dr. Golomb questioned whether the squalene study in the draft recommendations would address the question of whether anthrax-vaccinated veterans have higher levels of squalene than nonanthrax-vaccinated veterans. Dr. Steele stated that this should be specified. Also, it could be suggested that the focus be narrowed to specific lots of vaccine. Dr. Golomb noted that Dr. Alving had earlier published a specific position on this issue before having data.

Dr. Steele noted that the third recommendation had an asterisk by it. In the last few weeks, a paper was published on results from the Millennium Cohort Study, a prospective study of individuals in the military, from different eras. The Committee was not aware of this project at the time of its last recommendations. This study will be asking individuals whether they have had the anthrax vaccine or not and will also have access to DoD medical records indicating whether or not personnel received the anthrax vaccine. In a sense, the Millennium Cohort Study addresses, to some extent, the recommendation for longitudinal assessment of personnel who received anthrax vaccine adsorbed (AVA). This study will not look at symptoms specifically, but will use SF-36 measures for different domains. There initial report found no difference between AVA recipients with respect to SF-36 measures. However, she knows that their questionnaire provided data on symptoms. Thus, the Committee's recommendation could be meaningfully addressed with data that already exist. She thought it would worthwhile to modify the recommendation to suggest a study using these data.

Dr. Melling noted that it should not be forgotten that there were two distinctly different anthrax vaccines used during the first Gulf War. The U.S. used one version, while the U.K. used the other. These were produced by different manufacturers and via different methods of manufacturing. Because both vaccines were given to a large number of troops, he thought the data could be useful in trying to assess the extent of the impact, if any, of these vaccines rather than "an" anthrax vaccine. Dr. Steele agreed and noted that it had been suggested that active antigen was the culprit within the vaccine. Dr. Golomb noted that another issue concerned several quality control issues surrounding the production of the Gulf War anthrax vaccines. Dr. Steele stated that these problems could be described in the narrative. Dr. Golomb stated that her point was that any data from current vaccinations are qualified by the fact that if they do show something, they have implications for Gulf War veterans. However, if nothing is revealed, it doesn't completely close the issue with respect to the earlier vaccinations. Dr. Steele noted that, in theory, there were some groups of veterans who are known to have received AVA in the Gulf War. Dr. Kang's study included a small number of these veterans. However, this information is hard to capture. Dr. Nettleman indicated that caution should be used in the wording of Dr. Golomb's point.

During the review of the neurotoxin section, Dr. Meggs suggested being more specific when referring to pesticides of concern. He also suggested a discussion of solvents. Dr. Steele noted that there was another chapter which discussed issues related to solvent concerns.

Dr. Clauw commented that there were individuals who would be looking for things in the report that they viewed to be scientifically inaccurate, and would use these to trash the integrity of the entire report. He thought the draft statement made with respect to sarin still was stronger than the data supported. He said that he had just run a PubMed search with respect to Khamisiyah and sarin, and all of the published epidemiological studies say the same thing. Some on the Committee disagree with how the plume was calculated, and this was a legitimate concern. Dr. Steele noted that few studies had looked at the relationship of multisymptom illnesses to Khamisiyah. Dr. Clauw acknowledged this and indicated the data were stronger for PB and other things. However, he thought if the Committee backed away a little more from sarin, then the report would less likely be criticized. Dr. Steele agreed and indicated that she had tried to convey this. The epidemiological data with respect to sarin was not strong. Dr. Clauw agreed that these weaknesses were addressed in the narrative, but not reflected in the list of specific recommendations. This will be a very contentious point in the report. Dr. Steele agreed that the

Committee wanted to accurately reflect what the science showed. She suggested that while the neurotoxins were combined in the discussion, the level of importance of the different compounds could be more explicitly noted. Dr. Meggs commented that Dr. Heaton's findings were good evidence on this point. Dr. Steele noted that this group had also looked at neurocognitive function. Dr. Clauw commented that there were also problems with this particular study that could be discussed too. Dr. Golomb added that there were a lot of problems with any sarin study because of the lack of good exposure data. She thought it was important to accurately reflect that the quality of evidence could never be good because of the lack of this data. It isn't that there is good quality of evidence that sarin is unrelated, but that the quality of evidence can will always be limited by the lack of good exposure data. While we acknowledge this point, we also know that some veterans were exposed and exposure could contribute to health problems if acetylcholinesterase inhibition contributes to health problems. Thus, this area of research is relevant to Gulf War veterans and the issue should be explored scientifically, even though the epidemiology from this issue will never be good.

Chairman Binns noted that the Committee's last report also made an effort to characterize the associations of pesticides and PB with Gulf War illnesses as stronger than sarin. He thought that an even better job could be done in this report. However, if the Committee were to take something like this out when looking at the different types of neurotoxins, this would draw as much attention as leaving it in the report. If there has been a change in the science in the last two or three years, it had been in the direction that sarin was a possible exposure of concern. He noted the Iraq Survey Group's findings regarding possible releases during the 1991 Shia' revolt, along with the two studies presented to the Committee the previous day. He stated that there was another study that would be made public at the American Academy of Neurology's conference the following week.

Dr. Golomb commented that, even if the Khamisiyah plume were accepted, many of the individuals in the unexposed group may have been exposed in other settings. Thus, considering them as an "unexposed" population will not necessarily lead to reliable results. Dr. Nettleman commented that the argument being made seemed to suggest that this question was impossible to study. Dr. Golomb stated that it may be impossible to study the epidemiology, but this did not limit consideration of other evidence of a plausible cause-and-effect relationship that could be relevant to Gulf War veterans. These lines of research should be pursued given triangulated evidence that the mechanism is relevant. Dr. Nettleman stated that there were many reasons to continue studying sarin, and thought it should be emphasized that we will never be able to tell who was exposed or not, or the level of exposure for those exposed. If we are talking about causality or association, sarin is an important area of research that may also relate to Gulf War veterans. Dr. Steele asked if the suggestion was that since a good epidemiologic study on this point couldn't be done, it shouldn't be attempted. Dr. Nettleman stated that she thought this could be true, and that results from such studies could be a distraction. She agreed with Dr. Clauw's point of two levels of association.

Dr. Steele noted that despite press reports, the 2004 Committee report had not concluded that sarin caused Gulf War illness. It said that that there was evidence that neurotoxins, as a group, were linked to Gulf War illness. Dr. Clauw commented that a different impression had been conveyed to some researchers.

Dr. Golomb stated that she would not have a problem separating out cholinesterase inhibitors in the present report, but didn't have a problem with either approach. Dr. Melling commented that we should not lose sight that some people involved in the Gulf conflict were exposed to low levels of sarin, while those who were not involved were not exposed. While we don't know the number of individuals exposed to sarin in the Gulf theater, this does not detract from the fact that we know that individuals were exposed.

Dr. Clauw noted again that this will be the part of the report that will be most scrutinized by some people. However, he believed that it could be crafted or "wordsmithed" so that it is clear that this is a potential problem, but the weight of the evidence is much greater for PB and pesticides than it is for sarin. Other members agreed with this point.

Chairman Binns stated that he had assumed until four months ago that there would never be any human data on sarin exposure from the Gulf War. However, using DoD exposure estimates, there are more data now than was envisioned. Dr. Golomb commented that she remembered one particular study that found those involved in the demolition of Khamisiyah did have higher rates of illness. However, when the study was published, a broader exposure group was used which diluted the findings. This study did show that those who were more likely to be exposed to sarin had more health problems. Dr. Steele stated that a caveat would have to be included that analyses of the Khamisiyah plume, without controlling for other exposures, will also affect the outcomes. Dr. Clauw noted that the research presented the previous day looked at multiple exposures, which they should continue to do. The research should focus exclusively on sarin. Rather the outcomes of interest, e.g., brain imaging, neuropsychological, etc., should be examined and related to a variety of exposures, which was the approach most scientifically and politically neutral.

Chairman Binns thought that there may be a way to fine tune the language, with a specific idea in mind, to steer the UTSW program towards the most productive work. Dr. O'Callaghan noted, throughout the report, the flow is to go from single agents to combinations. This should be an enduring theme throughout the report. Dr. Clauw asked why a researcher looking at an animal model would want to use sarin versus organophosphates given the difficulty of administration. Dr. Steele stated that Dr. Haley was focus on this particular exposure because he had studied a cohort that had a possible exposure to sarin. His findings with this group showed a huge risk factor related to a specific event. Dr. Clauw noted that the group studied by Dr. Haley was very small in comparison to the entire Gulf War veteran population.

Chairman Binns commented that he is always asked by the public about the effects observed in the local population. While there haven't been good studies conducted on this population, he imagined if there was an illness affecting 25 percent of Kuwaitis or Saudis, it would be known. Dr. Golomb disagreed. She stated that she had visited Kuwait and Saudi Arabia in 1997 and talked with health administrators about whether they were seeing any illness. She noted that, even in the US, everyone was saying there was no excess in illness until formal epidemiological studies were done. She stated that there was no tradition of doing this type of science over there. She would talk to some health professionals who said that they saw nobody with these health problems. However, even a control group would contain some people with these conditions. When she would talk with the local physicians and US citizens working over there, they would report seeing these conditions all the time. Dr. Steele noted that the Harvard School of Public Health Kuwaiti study would help answer some of these questions. She indicated that the researchers were very open to adding some multisymptom illness questions to their survey, so there will be population data on the health of Kuwaitis.

During the review of the infectious diseases section, Dr. Golomb asked for clarification about the brucellosis issue. Dr. Steele stated that there were no data on whether this might be a possible contributor to Gulf War veterans' health problems. She noted that there were tiny groups of veterans examined for brucellosis, but there were no data from larger studies. Dr. Steele explained that brucellosis was a bacterial disease that can cause chronic disease similar to that seen in Gulf War veterans. She stated that there were reports of a brucellosis epidemic in the region prior to the Gulf War. While the normal transmission is through contaminated milk and food products, it can be transmitted in other ways. She noted, though, that it was difficult to make specific recommendations when there is nothing known about it. She indicated that Chairman Binns and she had been approached by a microbiology technician at a VA

hospital who had stool samples from individuals he suspected had brucellosis. This was the only lab information she had heard on this point. Dr. Clauw indicated that he could share information about this from Michigan.

Chairman Binns asked whether the question of opportunistic infections that might be addressed would be covered in the text. Dr. Steele stated that infectious agents, e.g., herpes viruses, that had been associated with other chronic multisymptom illnesses had only minimally been looked at in Gulf War veterans, and that it was difficult to say which ones should be investigated. There are only limited data showing that symptomatic Gulf War veterans have increased rates of infection. Chairman Binns commented that there was a recent Stanford study that showed patients whose chronic fatigue was associated with elevated Epstein Barr and other herpes viral loads were successfully being treated with an antiviral drug. While a separate study would not be justified, it might be something to look at when veterans are being studied anyway.

Dr. Steele stated that cross sectional serology studies haven't consistently shown a connection of CFS with herpes virus infection. She didn't know if the Committee wanted to tie this line of research into the report. She wondered if this might fall under the recommendation that any treatments found to be beneficial for chronic multisymptom illness should be considered for Gulf War veterans. Chairman Binns noted that this would be something that could be objectively tested in veterans. Dr. Steele noted that Drs. Natelson and Vojdani had studied herpes virus infection rates in Gulf War veterans. Dr. Natelson had done polymerase chain reaction (PCR) testing of herpes viruses and Dr. Vojdani had done serology on a clinical sample. Dr. Natelson did not find any elevation of herpes virus in ill Gulf War veterans but did find slight elevations in chronic fatigue syndrome patients. But the ideal study to address this issue had not been done. She thought this was an issue of interest but asked for guidance from the Committee as to how to address it in the report. Dr. Golomb stated that one could look at these as markers and possible treatment targets. However, even if they are present, we don't really know to what degree they contribute causally.

With respect to Epstein Barr virus, Dr. Melling noted that most individuals in their late adolescence or early adult lives are exposed to this virus. A few of these individuals do not have a good spontaneous recovery. He wondered if the antiviral treatments were targeted at the individuals with poorer recovery. In terms of Gulf War veterans, it may be possible to compare the incidence of infection based upon immunology. This would depend on having blood samples collected from the time of the Gulf War, because people who weren't infected then may have since become infected. Dr. Golomb noted that some Gulf War epidemiologic studies had reported increased rates of respiratory infections. While relevant, it is unknown whether these are markers for an impaired immune function. Chairman Binns wondered if these could be added to the list of tests done when Dr. Haley processed his blood samples. Dr. Steele agreed that herpes viruses could play a role, but again indicated that the New Jersey study of Gulf War veterans had not found herpes viruses to be an issue. Dr. O'Callaghan commented that it would be easy for Dr. Haley to just do it. Dr. Steele thought that this point could be included in the chapter on the biology of Gulf War illness, looking at possible tests that might identify differences between sick and healthy Gulf War veterans.

During the review of Section 3 of the report, Dr. Steele commented that, contrary to common assumption, rates of all multisymptom illnesses were not higher in Gulf War veterans than the general population. The rate of defined chronic fatigue syndrome is the highest of any documented in a defined population but fibromyalgia and MCS rates are more comparable to the general population. However, because Gulf War veterans are predominantly a population of young males, the rates of these conditions are likely higher in Gulf War veterans than in nonveteran males of comparable age. Dr. Meggs noted that another important caveat was that the percentage of individuals who self-reported MCS is much lower than the

percent that actually have it. This is due to the masking or adaptation phenomenon where they have chronic illness associated with exposure but no acute reactivity. Dr. Steele wondered if the proportion of people whose MCS symptoms were obscured by masking would be comparable in Gulf War veterans and nondeployed veterans. Dr. Meggs thought this would probably be true. Dr. Steele stated that MCS rates were probably higher in Gulf War veterans but not to the same extent as chronic fatigue syndrome. Dr. Golomb noted there was one study that showed a specific association of MCS in Gulf War veterans with pesticide exposure. Dr. Steele said that this UK study was quite interesting. Very few MCS or CFS studies have looked at relationships with exposures, but this one did and found an odds ratio of 12 for pesticide exposure in relation to MCS.

During the discussion of recommendations regarding Gulf War illnesses in relation to multisymptom conditions in the general population, Dr. Golomb suggested that the summary make note of studies that have shown that Gulf War veterans who meet the definitions for these conditions differ from nonveterans who meet these definitions. Dr. Steele indicated that those would be included.

Dr. Golomb also raised the issue of being more specific with regard to recommendations about enzyme research in relationship to multisymptom conditions. She mentioned an animal study that found alterations in protein expression in the brain following organophosphate exposure. Another study had found that MCS patients with a specific type of sensitivity had depressed levels of the enzyme that helped clear that toxin from the body. For example, if the individual had a sensitivity to formaldehyde, they had depressed levels of the enzyme that helps clear formaldehyde from the body. She wondered if the Committee might make a recommendation that research be conducted that looked at the relationship between exposures and the concentration of enzymes that clear toxins. Dr. Steele noted that recommendations regarding metabolizing enzymes had previously been made in a more generic way, as were the ones that exposure subgroups be examined. She indicated that discussion of the studies mentioned by Dr. Golomb could be included in the text of the report, but wondered if it should be included in the recommendations too. She thought the point made by Dr. Golomb was important, but didn't want to diminish the importance of the need to look at exposure subgroups with respect to all biological variables by singling out metabolizing enzymes. Dr. Golomb indicated that it might be worth suggesting that there was specific interest in pesticide exposures in relation to concentrations of enzymes that clear those compounds. Dr. Steele agreed and noted that there were some data that indicated that deployment to the Gulf War had resulted in reduced PON1 activity levels. So, even looking at exposure in the most generic way, i.e., deployment to the war, there may be findings along those lines. And if one were to focus in on specific exposures, one might potentially find more.

Chairman Binns expressed his hope that discussion concerning recommendations pursuant to the previous day's presentation could be discussed at the next Committee meeting.

Chairman Binns asked whether an additional comment and/or recommendation should be added concerning the PET scan research discussed by Dr. Tomas Guilarte at a previous Committee meeting. Dr. Steele stated that this would seem to be covered by the recommendation for "studies that evaluate alterations in central proinflammatory and inflammatory processes in Gulf War veterans." Chairman Binns agreed but also stated that he was comfortable being more specific in recommendations when the Committee believed that a particular study should be conducted. This would make things clearer for researchers. Dr. Steele agreed and added that the wording could be such that other measures could also be specifically identified.

Chairman Binns commented that Sections 4 and 5 recommendations appeared to be summary points and wondered if these points could be discussed at the next meeting. Dr. Steele noted that part of the purpose

of reviewing these recommendations was to allow members of the public in attendance to hear them and comment if they so wished. Chairman Binns acknowledged this and asked Dr. Steele to continue.

During the discussion of the recommendation concerning funding to UTSW, Dr. Golomb expressed concern about recommending that the entire $15 million of VA funding be appropriated to one institution. She believed that research funds should be open to all researchers, such as Dr. Paul Greengard or Dr. Wallace, and shouldn't be focused at one site because it restricts the potential for advancements that could be made. Dr. Steele referred to the recommendation that Congress appropriate $30 million to the CMRP program, and suggested that this might compensate for this. Dr. Golomb noted that the VA UTSW program allocation would put one third of the Gulf War illnesses research funding at one site, which has a specific vision about the cause (sarin) of Gulf War illness. She stated that while she thought sarin research was important, she didn't think this was the best way for funds to be appropriated. Chairman Binns thought this was a good point, and one that should be discussed further at the next meeting. Dr. O'Callaghan noted that there were pros and cons for all of the recommendations that could be discussed at the next meeting.

Dr. Steele noted that there was also a recommendation that VA ORD continue to solicit and fund additional Gulf War research studies through Gulf War-specific funding announcements. She also noted that Dr. Goldberg had just informed the Committee that there were no plans to continue to do this. Dr. Goldberg commented that if $15 million of VA research monies go to UTSW, there were no additional funds for these RFAs. Dr. Steele said that the Committee had originally understood that $15 million was earmarked for UTSW, in addition to the usual annual amount allocated for ORD funding. Dr. Goldberg stated that there was only one research appropriation budget, and with $15 million going to UTSW, there was nothing left in the budget to do more Gulf War research. Rev. Graves commented that his understanding was that the $15 million earmarked was an additional appropriation of monies. Chairman Binns stated that, from his perspective, the Committee asked Congress to appropriate $15 million to VA which they did. Congress earmarked it, however, for research at UTSW. He thought that it would be good to continue pressing VA to do the things that they were set up to do, e.g., ALS and other illness registries, long-term epidemiological studies, etc. He thought it was too soon to ask for "another bite at the apple" now that they have given us "the bite" for which we have already asked. Dr. Golomb stated that she didn't recall ever being a part of a recommendation that all $15 million go to one site. Chairman Binns agreed that the Committee was not part of that decision, but this was a different issue.

Dr. Steele noted that that the Committee had understood that there was a possibility that the ALS registry and brain-tissue bank would no longer be funded, therefore had made a recommendation that this funding continue. She noted that the current recommendation would suggest that these focus more specifically on Gulf War veterans as opposed to such a large percentage of non-Gulf War veterans. She noted that: (1) there were currently only 50 Gulf War veterans represented in a registry of 1,500 veterans; and (2) Dr. Oddone had reported that the registry could be expanded to include other neurodegenerative diseases.

During the discussion of the priority research topics in Section 5, Dr. Golomb suggested that the fourth recommendation be modified to say "epidemiologic research carefully characterizing ongoing outcomes in Gulf War veterans with particular attention to…" Dr. Steele noted that there was a lower priority section that recommended the monitoring of several conditions, such as cancer. Dr. Golomb commented that this all might be able to be done in the same recommendation. Dr. Steele commented that if Dr. Haley wanted to assess in his large epidemiologic study whether individuals had neurological diseases, cancer, asthma, etc, he would be able to ask them but he would not be able to carefully characterize their conditions. She questioned whether the recommendation should be defined along these lines. She thought the characterization for neurological diseases was more important because this was where the "gray area" was. Dr. Golomb noted that simply stating "epidemiologic research" didn't imply careful

characterization. Dr. Steele asked Dr. Golomb if she thought then this should be folded in with all of the other diseases, i.e., a recommendation for a study that identifies specific diagnoses. Dr. Golomb noted that researchers could look at the veterans' diagnoses, and that there, for example, had been no investigation as to the rate of Parkinson's disease in Gulf War veterans. Dr. Steele agreed that this research hadn't been done but was very important. She wondered if the recommendation should be that researchers should determine the rate of various diagnoses or conduct a more-detailed in-depth assessment of neurological diseases. The first "pass" is to find out which conditions have been diagnosed in Gulf War veterans, and then bring them in for evaluation. Dr. Golomb stated that epidemiological research implies the review of the records or surveying veterans. It does not imply in-depth assessments. She agreed that the first step shouldn't involve an in-depth evaluation so that the broad picture could be seen. This would provide information to better focus future research.

Following discussion of Section 5, Chairman Binns thanked Dr. Steele for her efforts in drafting the Committee's recommendations and report. He noted that it was extremely challenging to summarize all of this work in one document, and the Committee was fortunate to have someone who is able to do this. He thanked the Committee as well for good discussions about the recommendations and report.

Public Comment – Day 2

Capt. Richard Johnson, who is the British liaison to the VA, stated that he had recently spoken with Dr. Mark Brown about the Gulf War Review. He reported that Dr. Brown had confirmed to him that the VA Environmental Agents Service intended to issue this newsletter in both electronic and paper copy.

Chairman Binns thanked Capt. Johnson.

Ms. Venus Val Hammack, a Gulf War veteran, spoke to the Committee. She stated that, after 15 years, Gulf War veterans were still not being adequately treated. While Gulf War veterans may have a registry exam that looks at their industrial and infectious disease exposures, only 50% are being sent for Phase Two examinations. The numbers dropped off even more with respect to Phase Three and family examinations. Another issue is that while veterans may see internal medicine, neurology, gastroenterology, and respiratory specialists, less than 10 percent of the veterans had been seen by an industrial hygienist. Another problem is the lack of referrals to infectious disease specialists. American physicians are not familiar with many of the diseases that Gulf veterans were exposed to in the Middle East. This will stymie the data and information needed to develop the proper research recommendations.

Ms. Hammack also noted that another stumbling block for veterans was VA's Office of Environmental Agents. A lot has been determined about Gulf War illness and the specific symptoms that should be evaluated. But the Office of Environmental Agents has not distributed this material, the Gulf War heath guidelines, or clinical guidelines. This had previously been conveyed to VA clinical staff by continuing education classes and materials. This has not existed in the last three years. Therefore, she could not pick up this material and take it to her physician because it is three years old. At the time it was released, she could find it in the hospital library or the director's office. However, it was no longer located in a Gulf War clinic, which no longer exists. The closest thing to current information on Gulf War health issues now is the Committee. Ms. Hammack said that the Environmental Agents office also impacts communication to VA facilities about the Committee's existence. There is little information available at the individual medical facilities. A veteran also has to know to look for an Environmental Agents coordinator, not a Gulf War coordinator. This is not intuitive to the average veteran. These coordinators also are wearing many different "hats." The veterans are not getting to the registry, the infectious disease specialist, the industrial hygienist, etc., to evaluate their symptoms.

Chairman Binns thanked Ms. Hammack.

Ms. Denise Nichols, a Gulf War veteran, spoke to the committee. She indicated that she had a long list of points to make regarding the recommendations reviewed during the meeting.

With respect to autoimmune disorders, she suggested that these be tracked in Gulf War veterans. If there is a problem with the vaccines, it might be reflective of autoimmune disorders. This could be tracked by the Veterans' Health Administration. She also suggested that, based on the discussions of ALS and MS, early development of Alzheimer's disease might also be of concern to Gulf War veterans. She thought wording regarding this should be included. With regards to tracking cancer rates, she noted Dr. Steele's earlier comments about the current use of state registry data. She noted that every hospital is supposed to have a tumor board, which is a part of the VA hospital accreditation standards. She thought a review of the VA tumor boards should be undertaken to ensure that they are collecting this data with respect to Gulf War veterans. With respect to birth defects, Ms. Nichols noted the discussion of behavioral issues in children of Gulf War veterans. She stated that they were seeing a lot of autism in these children. Ms. Nichols also suggested reviewing what the Comprehensive Clinical Evaluation Program (CCEP) did with the EEG, EMG, and other data collected that she didn't believe had been reviewed collectively. She noted that this review would be a retrospective study.

With respect to psychological concerns, Ms. Nichols stated that many Gulf War veterans seem to be being diagnosed with bipolar disorder. She wondered if VA data could be collected to identify the rate at which this was being diagnosed in Gulf War veterans. She wasn't sure why this might be happening. With respect to sand and fine particulate matter, Ms. Nichols thought that possible silicosis was being forgotten. This could play a role in the development of the diseases. She also stated that some of the problems were due to policy, which was not addressed in the report. She thought that many of problems resulted from policies set from "on high" and suggested that a review of research policy at the higher levels of VA be conducted.

Ms. Nichols noted that leishmaniasis can remain dormant. Also sixteen years has now elapsed since the Gulf War, which is important with respect to cancer development. She commented that the current troops' exposure to depleted uranium needed to be kept in mind. There should be a mention of the need to track OIF/OEF veterans' conditions which might be associated with exposure to depleted uranium. She suggested a paragraph or two at the end that highlighted the current troops' situation. Depleted uranium research should also focus on the development of the best detection test. It should be determined whether the current DoD test, Dr. Durakovic's test, or the chromosome test is the best testing method. Also important is determining the time at which the test should be conducted. With respect to the lack of data on infectious diseases, Ms. Nichols suggested that a discussion of the interaction between research and clinical interests be discussed at this point of the report. She thought that there were exploratory/small types of research studies that could be conducted in the clinical areas. These types of studies would not cost as much, and monies could come from the clinical care fund.

Ms Nichols announced that there would be a June 7-10, 2007, meeting hosted by Dr. Rhea and Giles that focused on the autonomic nervous system. She also suggested that the Committee's July 2007 meeting be held in Arizona or Boston, where the Gulf War brain bank was being set-up and developed. Ms. Nichols also asked that Committee members contact their representatives and senators to request they link the Committee's and/or Gulf War research funding sources websites on their respective Congressional websites. This would encourage researchers in their states to pursue these opportunities, which would bring more monies back to their individual states. She noted that the Fitzsimmons VA facility, in her home state of Colorado, was becoming a biomedical research park. She thought this might be a possible

location for an upcoming Committee meeting. This might encourage more research into this field by researchers in this growing center.

Chairman Binns thanked Ms. Nichols for her suggestions and comments.

Chairman Binns commented that the tentative location for the Committee's July 2007 meeting was Dallas, Texas. This is where a great deal of VA funded Gulf War research is being done, and the Committee would like to hear more about what the researchers are doing. He thought it would be a good idea for the Committee to visit this location at least once a year. He noted that the October 2007 meeting would then be held in Washington, DC, for the release of the Committee's report.

He thanked everyone for their patience and participation.

The meeting adjourned at 1:40 p.m.