Research Advisory Committee on Gulf War Veterans' Illnesses

February 23-24, 2004 Committee Meeting Minutes

U.S. Department of Veterans Affairs
811 Vermont Ave, Room 819
Washington, D.C.

DEPARTMENT of VETERANS AFFAIRS

Research Advisory Committee on Gulf War Veterans' Illnesses
VA Eastern Kansas Healthcare System (T-GW)
2200 S.W. Gage Blvd. Topeka, KS 66622

I hereby certify the following minutes as being an accurate record of what transpired at the February 23-24, 2004, 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 in Attendance
James H. Binns, Chairman
Nicola Cherry
Beatrice Golomb
Joel Graves
Robert W. Haley
Marguerite Knox
William J. Meggs
Pierre J. Pellier
Steve Robinson
Steve Smithson
Lea Steele

Consultant to the Committee
Jack Melling

Committee Staff
Laura Palmer

Guest Speakers
John Concato
Roger Kaplan
Preeti Hans
Joe Gough
Alan Magill
Ya Fang Liu
Mohan Sopori
John Ottenweller
Mark Peakman
Al Marshall
Terry Pellmar
Johnnye Lewis
Melissa McDiarmid
Sam Donta

Abbreviations

AChE	Acetylcholinesterase
AFRRI	Armed Forces Radiobiology Research Institute
BLRD	Biomedical Laboratory Research and Development service (VA)
CFS	Chronic fatigue syndrome
CSRD	Clinical Science Research and Development service (VA)
CRADO	Chief Research and Development Officer (VA)
DHI	Deployment Health Initiative
DoD	Department of Defense
GAO	General Accounting Office
GWI	Gulf War illness
NSF	National Science Foundation
OEF	Operation Enduring Freedom
OIF	Operation Iraqi Freedom
ORD	Office of Research and Development (VA)
PB	Pyridostigmine bromide
PI	Principal investigator
VA	U.S. Department of Veterans Affairs

Meeting Agenda

Monday, February 23, 2004

8:30 – 8:45	**Welcome, introductions, and opening remarks**	Mr. Jim Binns
8:45 – 9:15	**Update on ongoing VA Gulf War illness research projects** *Dr. Concato, director of the Clinical Epidemiology Unit at West Haven VAMC, will provide an update on VA's study investigating levels of a mutant form of acetylcholinesterase (AChE-R) in ill Gulf veterans. Mr. Kaplan will report on other VA Gulf War illness research projects of interest.*	Dr. John Concato Mr. Roger Kaplan
9:15 – 9:45	**Research funded under the Deployment Health Initiative** *Ms. Hans is staff assistant for Gulf War illnesses in VA's Office of Research and Development. She will update the Committee on proposals received and projects funded under VA's Deployment Health and Cooperative Studies funding announcements.*	Ms. Preeti Hans
9:45 – 10:15	**Overview of VA administration of Gulf War illness research proposals, review, and funding** *Mr. Gough is Acting Director of Administration in VA's Office of Research and Development. He will discuss how Gulf War illness research proposals are scientifically reviewed, funded, and prioritized, and provide additional information on the $20 million Deployment Health funding initiative.*	Mr. Joe Gough
10:15 – 10:30	***Break***	
10:30 – 11:00	**Discussion**	
11:00 – 12:00	**Leishmaniasis in veterans of Desert Storm and Iraqi Freedom** *Dr. Magill is Science Director at the Walter Reed Army Institute of Research. He will provide an overview of detection and assessment of leishmania infection in Gulf War veterans, and preliminary information regarding leishmania infection in military personnel serving in the current conflict in Iraq.*	Dr. Alan Magill
12:00 – 1:00	***Lunch***	

1:00 – 1:45	**Role of stress-activated kinase in the pathogenesis of Gulf War Syndrome** *Dr. Liu is an Assistant Research Professor of Pharmacology at Boston University. She will discuss her research on the induction of mixed lineage kinases and neuroinflammation by stress, vaccines, and pyridostigmine bromide, and the potential use of kinase inhibitors to prevent or treat the adverse consequences.*	Dr. Ya Fang Liu
1:45 – 2:30	**Immunotoxicity of low-dose sarin and silica inhalation** *Dr. Sopori is Senior Scientist and Director of the Immunology Program at Lovelace Respiratory Research Institute. He will present results of his studies investigating immunological effects of inhaled exposure to sarin, sand, and cholinergic agents such as pyridostigmine bromide.*	Dr. Mohan Sopori
2:30 – 2:45	***Break***	
2:45 – 3:30	**East Orange VAMC research on immune parameters in ill Gulf War veterans** *Dr. Ottenweller is a Professor of Neurosciences at the University of Medicine and Dentistry of New Jersey. He will discuss studies at the East Orange VA Center for Environmental Hazards Research on lymphocyte subpopulations and cytokine levels in symptomatic and healthy Gulf veterans.*	Dr. John Ottenweller
3:30 – 4:30	**Immune activation and Th1/Th2 cytokine balance in Gulf War-related illnesses** *Dr. Peakman is with the Department of Immunobiology in the School of Medicine at King's College in London. He will present results of a study of cellular immune activation associated with multisymptom illness in British Gulf War veterans.*	Dr. Mark Peakman
4:30 – 5:00	**Discussion**	
5:00 – 5:30	**Public Comment**	
5:30	**Adjourn for the day**	

Tuesday, February 24, 2004

8:00 – 9:00	**Overview of potential health consequences of depleted uranium use** *Mr. Marshall is with Sandia National Laboratories in Albuquerque. He will provide an overview of possible concerns related to radiological and chemical effects of DU exposures in Gulf War veterans.*	Mr. Al Marshall
9:00 – 10:00	**Research on the effects of depleted uranium from the Armed Forces Radiobiology Research Institute** *Dr. Pellmar will report on the results of multiple studies conducted by investigators at the Department of Defense's Armed Forces Radiobiology Research Institute assessing the biological effects of implanted DU fragments in animals.*	Dr. Terry Pellmar
10:00 – 10:15	***Break***	
10:15 – 10:45	**Studies of the uptake and neurological effects of inhaled uranium** *Dr. Lewis is Director of the Community Environmental Health Program at the University of New Mexico. She will report on her research on the potential for inhaled uranium to enter the brain through the nose and cause neurological damage.*	Dr. Johnnye Lewis
10:45 – 11:30	**Surveillance of veterans exposed to depleted uranium during the Gulf War** *Dr. McDiarmid directs VA's Depleted Uranium Program at the Baltimore VAMC. She will present an overview of the results of the program's ongoing clinical surveillance of Gulf War veterans who have embedded DU fragments, DU-contaminated wounds, and significant inhalational exposure to DU.*	Dr. Melissa McDiarmid
11:30 – 12:00	**Discussion**	
12:00 – 1:00	***Lunch***	
1:00 – 1:30	**Overview of research on infectious diseases in Gulf War veterans**	Dr. Lea Steele
1:30 – 2:15	**Findings on mycoplasma infection and treatment from VA's antibiotic treatment trial** *Dr. Donta is a retired Professor of Medicine at Boston University Medical School and principal investigator of VA's antibiotic treatment trial. He will present findings from the study and discuss their implications with respect to the role of mycoplasma infection and antibiotic treatment in Gulf War veterans' illnesses*	Dr. Sam Donta
2:15 – 3:00	**Update on recently published research**	Dr. Beatrice Golomb

3:00 – 3:30	**Committee business**
3:30 – 4:00	**Public comment**
4:00	**Adjourn**

Welcome, introductions, and opening remarks

Mr. James H. Binns, Jr., Chairman

Chairman James Binns called the meeting to order at 8:30 a.m. He stated that he had high expectations for the Committee for three reasons:

1. Significant scientific progress made in last eighteen months by the people speaking at this and previous Committee meetings.

2. Progress by the Committee and its new staff organization, which was reflected in the quality of this meeting and preparation that had gone into it.

3. Changes taking place over the past two years at the Department of Veterans Affairs (VA). Chairman Binns cited the enormous support from Secretary Principi. He noted that, due to the Secretary's initiative, up to 20 million dollars had been committed to research for Gulf War illnesses. He also noted the development of a pattern, such as the work done with Dr. Soreq, where the Committee worked with VA's Office of Research and Development (ORD) to hand off an idea and see VA run with it.

Chairman Binns noted the loss of Dr. Nelda Wray as a champion within VA for Gulf War veterans. He expressed the Committee's gratitude for the contributions she made and extended well wishes in her future endeavors. He stated that the progress she began was going to continue, through new officials, like Dr. Jonathan Perlin, Deputy Under Secretary for Health and Acting Chief Research and Development Officer (CRADO). Chairman Binns read a message from Dr. Perlin, which was as follows:

"I would like you to know that Mindy (Aisen) and I emphatically support research into the illnesses of Gulf War veterans. I would ask for your help in conveying this message to the Committee as it is our desire to continue the tradition of collaboration, mutual respect and shared purpose."

Chairman Binns welcomed a joint effort between ORD and the Committee. He indicated that the pieces were in place, and it was time to start doing something about it. He stated that the Secretary expected it, along with 175,000 ill veterans. He stated that he believed this was a deliverable goal.

Chairman Binns asked Dr. Lea Steele, the Committee's Scientific Director, to say a few words. She introduced Ms. Laura Palmer, who joined the Committee's staff in December, 2003. She then asked Committee members to introduce themselves to the audience.

Chairman Binns introduced Dr. Mindy Aisen, Deputy Chief of Research and Development. Dr. Aisen is a Board-certified neurologist, a Fellow of the American Academy of Neurology, and President of the American Society of Neurorehabilitation, with special interests in multiple sclerosis and other neurodegenerative diseases.

Dr. Aisen gave a brief overview about the reorganization of ORD research services which was being undertaken to run a more fluid program. She stated that ORD was absolutely committed to the scientific peer review system, working to make it better by making sure the top experts in the field were reviewing grant applications with scientific rigor. She stated that ORD also was working with clinical and veteran communities to ensure research being funded was relevant and not duplicative of what other agencies are doing. She indicated that ORD actively had been recruiting a PhD scientist to oversee the Gulf War illnesses program. She stated that ORD understood that, while the causes still were not clear, people were

ill and that was ORD's obligation to find out what the etiology is, what the nature of the problem is, and what sort of treatments may be useful.

Acetylcholinesterase activity in Gulf War deployed and era veterans: February 2004 update

John Concato, MD, MS, MPH
Director of Clinical Epidemiology, West Haven VA Medical Center

Dr. John Concato gave a status update on a VA research study being conducted by a team that includes Bradley Doebbeling, MD, MSc (Indianapolis), Peter Peduzzi, Ph.D. (West Haven), Hermona Soreq, PhD (Jerusalem), Catherine Viscoli, Ph.D. (West Haven) and himself. (See Appendix A – Presentation 1.) The following three hypotheses were being tested:

1. Mood and anxiety symptoms are associated with selected blood enzyme levels

2. Deployed (vs. non-deployed) Gulf War veterans have lower capacity to increase blood acetylcholinesterase (AChE) levels

3. Veterans with (vs. without) symptoms of Gulf War Veterans Illness (GWVI) have lower capacity to increase blood AChE levels in response to challenge

Dr. Concato stated that all data and laboratory analyses had been completed. Analyses of the initial hypotheses had been conducted, with other analyses being considered at this time. He indicated that the splice AChE-R data should be available by the next Committee meeting.

Dr. Beatrice Golomb suggested that it will be important to compare veterans who meet the CDC case definition for multi-symptom illness to veterans who consider themselves healthy, that is, who don't have any of the CDC symptom criteria. She also questioned one of the study's hypotheses, stating that one would not necessarily expect to see a reduced level of AChE in ill veterans exposed to AChE inhibitors. She stated that it was important to compare AChE levels in ill Gulf veterans who report AChE exposures, as opposed to all ill veterans, regardless of exposure, as combining all veterans could dilute findings that might otherwise be significant. She was encouraged to see that future analyses would include an examination of exposures.

Dr. Steele noted that Dr. Soreq had reported, at the October 2003 Committee meeting, an increase in acetylcholinesterase in Gulf war veterans compared with the normal population. She inquired as to whether this remained true. Dr. Concato stated it did, but all characteristics of the population needed to be accounted for before making assumptions about any differences. The Heritage Family Study was not a random sample of the U.S. population. Researchers didn't have access to all variables when this study was discussed in October, 2003. Further analyses, including these variables, were on-going.

Dr. Pierre Pellier inquired as to the proportion of ill veterans with anxiety disorder in the study's sample. Dr. Golomb inquired as to whether adjustments had been made for anti-depressant medication use. Dr. Concato indicated that they had, and there was little variation in the results.

Dr. Nicola Cherry inquired as to how the researchers were conducing validity checks of the self-reported exposures. Dr. Concato indicated that his group was being cautious by looking at the Iowa study's original questions to see if the questions looked at the same exposures, time served in Gulf, etc.

Dr. Golomb inquired as to whether the researchers would be able to ask "de novo" whether the Iowa study's reported symptoms did match CDC criteria, and if not, noted this might lead to misclassification and dilution of findings. Dr. Concato stated a "de novo" review was outside of the scope of this study, but they were aware of this concern and would be addressing in future reports how they were able to match the symptoms, as best as possible, to the CDC criteria.

Dr. Robert Haley inquired as to whether Dr. Soreq had calculated the alloenzyme concentrations of paraoxase and arylestease. Dr. Concato stated he would check into this.

Dr. Concato's talk concluded.

Dr. Aisen informed the Committee that Dr. Perlin was at an international meeting in New Zealand. The focus of this meeting was to develop a tighter collaboration between the US, UK, Canada, New Zealand and Australia with regards to Gulf War issues, including health. One of the plans is to develop a database that will be span these five countries. She stated that a follow-up research meeting was tentatively planned to take place in Hawaii.

VA Gulf War Illness Research Project

Roger Kaplan
Special Assistant, Central Office, VA Research and Development

Mr. Roger Kaplan provided the Committee with an update as to the recent reorganization within ORD. Previously, there was a large Biomedical Research and Development Service, charged with laboratory research and single-site clinical trials. Now, there will be two services: Biomedical Laboratory Research and Development (BLRD) and Clinical Science Research and Development (CSRD). CSRD will oversee all clinical trials [single and multi site (previously part of the Cooperative Studies section)]. Dr. Timothy O'Leary will be the new BLRD Director. A new CSRD director will be appointed soon. Two ORD services remain unchanged: Rehabilitation Research and Development Service and Health Services Research and Development Service.

Mr. Kaplan stated that ORD was in the process of re-announcing the Gulf War research specialist position. Besides his acting duties regarding Gulf War research, Mr. Kaplan primary duties entail Congressional liaison, veterans' outreach, biosecurity, biosafety, executive intra-correspondence, and inter-governmental relations.

Mr. Kaplan gave a progress report on Dr. Mike Weiner's Department of Defense (DoD) five-year study on the effects of Gulf War illnesses on brain function and structure. (See Appendix A – Presentation 2.) This study is a continuation of Dr. Robert Haley's research with the 24th CB battalion.

During discussion, Dr. Haley indicated that Dr. Weiner would be looking at several different case definitions.

Mr. Kaplan's talk concluded.

VA'S Deployment Health Initiative

Preeti Hans, MHP
Staff Assistant, Gulf War Illnesses, Central Office, VA Research and Development

Ms. Preeti Hans gave an overview of the Gulf War illnesses-related studies that had been funded through VA's ORD services. (See Appendix A – Presentation 3.)

Chairman Binns expressed dismay that only one study had been funded under the Deployment Health Initiative (DHI) since July 1, 2003. He stated that, of the sixteen studies funded/proposed as of last fall, only four studies really related to Gulf War illnesses. He noted that some of the other studies focused on stress hypotheses, although the Committee has pointed out that such hypotheses have not proven to be useful, as a central focus, in shedding light on Gulf war illnesses (GWI).

Mr. Kaplan stated that the ORD was also disappointed that only six proposals had been received under the DHI last fall. He indicated that the ORD would be doing more during the next proposal round to encourage field researchers to develop meaningful proposals. He cited reduced budgets contributing to the problem.

Dr. Golomb asked, in general, what percentages of the proposals were focused on stress vs. organic exposures. Mr. Kaplan stated that all three Clinical Biomedical proposed studies, which were denied, dealt with stress or anxiety. He stated that looking through the research portfolios, staff had identified GWI-related studies that had not been applied for under the DHI RFP. He stated that in terms of overall deployment-related studies, just over 9 million dollars had been committed.

Dr. Aisen noted the importance of understanding how a research program works and the many different relationships with various entities to produce quality work. She stated they needed to maintain credibility by funding projects that met the rigor of peer-review scrutiny. She discussed the scoring system and the need to improve the quantity of proposals, which would lead to a better quality of proposals. She stated that ORD was sensitive to the needs of deployed veterans and had decided to take other approaches to solicit more applications that are relevant to all of these types of conditions. She indicated that they didn't want to develop a program that lumped together diseases, e.g. neurodegenerative diseases, and call these "Gulf War illness." She stated their office needed to: (1) "prime the pump"; (2) identify potential researchers and the questions that they could investigate; and (3) encourage their service on review committees.

Chairman Binns stated this was good news, because the Committee had been hearing that, because of the failure to fund previous Gulf War related proposals, field researchers were discouraged about submitting additional proposals. He stated that Dr. Wray, the former CRADO, expressed intent to create a more pro-active program and was delighted to hear this stance would continue. He stated that he knew, from experience, research proposals needed to be designed to get to the particular goal, as opposed to acceptance of random proposals from field researchers.

Dr. Haley made a suggestion; based on his observations, the lack of proposals may be due to a lack of acceptance by many VA physicians that Gulf War illness exists. He suggested that the controversy as to whether Gulf War illness was a psychological, rather than organic, condition had handicapped the field. He wondered whether researchers didn't consider this field of study because they didn't believe it to be an organic illness, or perhaps they would be handicapped for expressing interest in the subject matter. He stated that this perception needed to be overcome, perhaps with some public relations to encourage field researchers' development of unique approaches to the problem.

Fall 2002 Deployment Health Solicitation and Review Process

Joe Gough, MA
Acting Director of Administration, Central Office, VA Research and Development

Mr. Joe Gough gave an overview of the Fall 2002 Deployment Health Initiative solicitation and review process. (See Appendix A – Presentation 4.) Mr. Gough noted that this solicitation remained open for additional proposals.

Dr. Steele asked whether there was a panel of people to review these applications with Gulf War illness expertise, or were the proposals assigned to boards that were not particularly familiar with Gulf War illnesses. She stated that there seemed to be no real prioritization given to Gulf War related proposals and that 20 million dollars had not been specifically set aside for Gulf War research.

Dr. Gough stated that Dr. Steele was correct; there was no specific Gulf War related illness review board. There were separate review boards for the Biomedical Laboratory and Clinical Sciences services. The Biomedical Laboratory Service, alone, has 21 sub-specialty specific boards.

Dr Aisen stated that there was a strong tradition within the VA research community. She indicated that Dr. Wray had provoked much controversy when she tried to introduce the notion of accountability and productivity to the review process. In retrospect, Dr. Aisen stated that these concepts probably weren't introduced gradually enough. She stated that the concepts needed to be introduced very openly and objectively. She stated that didn't mean ORD always says the recommendations of the advisory review panels are just that- recommendations from an *advisory* review panel. However, she stated that there was always going to be situation where the CRADO, once within the range of funded vs. unfundable proposals, had discretion in making final decisions. She stated that former Deputy Secretary Mackay had indicated that up to 20 million, not at least 20 million, dollars would be spent for Gulf War related illness. She stated that ORD had to be responsible with the funding decisions, keeping in mind that there are many of other important veteran medical concerns.

Chairman Binns asked if there was another avenue for the Committee and ORD staff to work together to develop a "top-down" research plan, rather than relying on general solicitation announcements. He believed that if field researchers knew there was money available, they might develop a proposal that would score high under peer review without sacrificing scientific quality, and achieve the ultimate goals relating to Gulf War illnesses.

Dr. Aisen noted that collaboration with advisory committees, like the Soreq collaboration, was fairly unusual within ORD. She stated that ORD was working towards building a more clinically-orientated research program. This process couldn't be sudden, and they were trying to encourage development of more clinical proposals in order to justify funding more of them. She wondered if there was a way to identify a certain set of treatment questions for Gulf War illnesses. She didn't want to single out researchers and ask them to write proposals because without competition, this might compromise the overall quality of the work.

Chairman Binns stated the Committee was trying to determine what was needed to stimulate VA GWI research. He stated that the veteran community saw the 20 million dollar funding initiative as a huge step forward, and that the science seemed to be there. Dr. Aisen agreed that genuine Gulf War research would grow in the future.

Mr. Joel Graves expressed his exasperation with ORD and its approach to the 20 million dollar funding initiative. He understood the Secretary's mandate made Gulf War illnesses research a top funding priority. If a proposal didn't meet scientific criteria, ORD would move on to other proposals. While the other proposal may be attractive and great science, Mr. Graves felt, if a proposal didn't met the primary criteria, its funding would be a misuse of research monies. Mr. Graves also believed that because the funding initiative was in response to the Committee and its recommendations, it was imperative that a representative(s) from the Committee be involved in the decision-making process.

Mr. Steve Robinson stated it was his understanding that the Committee, by Congressional charter, had federal oversight into anything and everything that had to do with Gulf War illnesses and federal Gulf War research, especially within VA. He asked whether a relationship between ORD and the Committee existed where the Committee was being made aware of what proposals were being submitted, and what, in terms of the Committee's concerns, was being done. He stated that discussions with the former CRADO had found an openness to create mechanisms whereby the Committee was in the loop as to what proposals were being received, what proposals were being funded, and where ORD stood in terms of approval of these proposals. He stated that he understood ORD's confidentiality concerns, but noted that there were scientific experts on the Committee that dealt with these concerns every day.

Dr. Aisen indicated that she thought there were mechanisms to create such a relationship. She stated that it wasn't unique for an advisory committee to want more of a role in the decision-making process, and that additional input was useful to the scientists.

Mr. Robinson stated he didn't expect to hold the new CRADO to the former CRADO's promises, but noted that this Committee had to answer to veterans. If the Committee didn't know what was going on, they wouldn't be able to respond to veterans' questions and concerns. He stated that even knowledge of proposal themes would help the Committee's understanding of funding statuses.

Dr. Aisen believed that the Committee would be pleasantly surprised with the proactive approach that ORD would be taking. She also believed there were still questions within the scientific community as to whether this was a syndrome that represented several problems or not. She acknowledged that the manifestations were different, but there wasn't enough scientific knowledge to say this was all basal ganglia regeneration, chronic infection, etc. Because of this uncertainty, it was difficult for ORD to say a proposal did or didn't relate to Gulf War illness.

Dr. Golomb stated that there was an acceptance that there are illnesses and there may be different exposures/factors. She expressed her concern that a core group of veteran advocates be given a confidential role into research.

Mr. Robinson stated that one of most troubling aspects of this situation is the Committee's lack of knowledge of current research funding. He told a story about being asked by a veteran about the Committee's accomplishments since it was appointed. He was able to list several things that had been done, but he also had to acknowledge what the Committee couldn't do because it hadn't had a view of the situation.

Chairman Binns indicated he had a similar interaction. He told a story about meeting with former Deputy Secretary Mackay after the June 2003 Committee meeting. Mr. Mackay asked a similar question: "How's the research coming? Are you getting some good research?" Chairman Binns had to respond that these were good questions, but he wasn't able to answer them. As such, former Deputy Secretary Mackay tasked Dr. Wray, former CRADO, to solve this problem. Chairman Binns stated that the Committee was glad to hear that ORD was not happy with the DHI solicitation process outcome, with respect to Gulf War

related research. He hoped that a solution could be found, taking into account ORD's confidentiality concerns, which would provide a closer meshing between the Committee and ORD, as well as a larger list of high quality proposals for funding that cover all development issues in the multiple illness consideration.

Dr. Aisen stated that ORD was working with field researchers addressing similar concerns, e.g., how review committees were chosen, how policy funding decisions were being made, etc. She reiterated ORD's openness to achieving more quality research.

Chairman Binns noted that Dr. John Ottenweller, a researcher from the East Orange, NJ, VA Medical Center, was in the audience. Chairman Binns asked Dr. Ottenweller if he could provide perspective as a VA researcher on the situation.

Dr. Ottenweller indicated that he could make two comments as to the ongoing discussion. First, he stated that field researchers had information from ORD that there was, in fact, no set aside funds or special review panel for the DHI. Thus, they were told there was no advantage to submitting a LOI under it. He stated there were researchers in his group that submitted half a dozen proposals relating to Gulf War illness that weren't included under the DHI. Dr. Aisen inquired as to the time frame for this information. Dr. Ottenweller stated it would have been in 2001, 2002 and early 2003. Dr. Aisen was surprised and requested more specific information, which Dr. Ottenweller offered to provide later.

Second, Dr. Ottenweller made a general comment about the "disconnect" between policy makers and the review board. He believed most people thought reviewers have criteria given to them to prioritize proposals but this wasn't always the case. From his experience on a review board, without an established list of administration policies, the individual reviewer's personal priorities may control their decisions.

Dr. Golomb noted there was scientific support for this. She stated that the NSF conducted a study, where they gave a set of proposals to independent review committees, and then compared the reviewers' scores. She stated that they found the concordance was a little better than chance. She agreed that, if you set aside factors on which to score things, an individual's perception of importance would vary.

Dr. Aisen noted that peer review was still an important aspect of funding good science. She did acknowledge that, while peer review was divine, the reviewers were human. She stated this just means "we" need to figure out how to improve the process. Dr. Aisen reiterated ORD's openness to improving the proposal process, making the portfolio more relevant, making sure the investigators care about veterans' concerns.

Chairman Binns expressed his appreciation for Dr. Aisen's interest in working with the Committee on these concerns. He noted that there was a psychological issue to the initiative being based on fiscal '04 funding. Being this was the year in which there finally was a commitment by VA leadership to address Gulf War illnesses, the Committee would like to capitalize on this momentum, and would be available in any way that would help.

Chairman Binns thanked ORD staff for speaking that morning.

The meeting adjourned at 11:00 a.m. for a ten-minute break.

The meeting reconvened at 11:10 a.m.

Leishmaniasis in veterans of Desert Storm and Iraqi Freedom

Alan J. Magill, MD, FACP
Science Director, Water Reed Army Institute of Research

Dr. Alan Magill provided an overview of the pathology, diagnosis and treatment of leishmaniasis. (See Appendix A – Presentation 5.) He discussed the diagnosed cases in Desert Storm/Desert Shield and Operation Enduring Freedom (OEF) and Operation Iraqi Freedom (OIF) veterans. He indicated that recent discussion about this disease, in connection with Desert Storm/Desert Shield veterans, was non-existent and welcomed a chance to revisit this matter, with a ten-year perspective.

With respect to OIF, Dr. Magill stated roughly 500 cases of cutaneous leishmaniasis (*L. major*) had been diagnosed. He indicated these cases were relatively easy to diagnosis (typical lesions) and were responding to therapy. He estimated that, based on what was being seen in the rotations coming out of Iraq, there would be over 1,000 cases, making this the biggest infectious disease problem in the current conflict. He did note that two soldiers who were stationed in Afghanistan had been diagnosed with visceral leishmaniasis the previous week.

Following Dr. Magill's presentation, Dr. Haley asked whether subclinical leishmaniasis might be a potential cause of the illnesses experienced by a portion of the ill Desert Shield/Desert Storm veterans. Dr. Haley wondered whether there might be a large group that may have potentially been infected, say, up to 20,000. Dr. Magill indicated that didn't fit with his observations of this disease in Desert Storm veterans.

Dr. Haley inquired as to what reliable tests were available. Dr. Magill stated that serology, with the current available antigens, was not helpful. From a basic pathogenesis point of view, he stated clinicians and researchers shouldn't spend a lot of time with this test. He would focus on CMI (cell-mediated response) testing for antigens that could be reliably detected.

Dr. Haley asked whether a skin test would be a reasonable way to test the hypothesis, in an epidemiological study, that leishmania was a cause of some Gulf War veterans' illnesses. Dr. Magill stated it would be helpful, but there currently was no reliable skin test available. He said that DoD had been developing such a test, but had halted the program in September, 2003. Dr. Magill stated that a cell-mediated immune response (CMI) test was a more viable solution. He noted there were on-going discussions to develop a CMI assay for leishmania, which was similar to the QuantiFERON assay for TB. Dr. Magill thought that, once a CMI test had been developed, it would make sense to go back and examine whether more Desert Shield/Desert Storm veterans were exposed to/infected with leishmania.

Dr. Haley noted, that in developing countries, treatment was given based upon symptoms, rather than clinical test confirmation, because of cost concerns. He asked whether it be reasonable to do a clinical trial, using one of the leishmaniasis treatments, with Desert Shield/Desert Storm veterans meeting the case definition of GWI. He stated this was a difficult call, but noted that some of these veterans' lives have been ruined. Dr. Magill stated that this option had been discussed, but that the side effects of the available drugs were potentially significant. He also expressed concern about controlling for placebo effects.

Dr. Mohan Sopori asked if research was being done to identify an immunological marker(s) to distinguish between various levels of leishmaniasis. Dr. Magill indicated that most of the immunological research on leishmania was general, using the parasite as a model organism. He stated that clinical outcomes were not an objective of most of this research.

Steve Robinson asked if all 500 OIF leishmaniasis cases had been evacuated from theater. Dr. Magill indicated that about 200-250 cases had been evacuated because they had multiple lesions.

Mr. Robinson asked what was the primary defense to leishmaniasis. Dr. Magill indicated that personal protection techniques (pesticides, mosquito netting, etc.) were used to protect soldiers from leishmania infection. Mr. Robinson asked if the anti-malarial drug had any effect on leishmania. Dr. Magill indicated that it did not.

Chairman Binns asked Dr. Magill for his thoughts and recommendations as to future leishmania research that would make sense for the ill veterans of the first Gulf War.

Dr. Magill indicated that he could envision a few hundred veterans having been infected, but not diagnosed. To develop a research approach with respect to these veterans, he indicated that he would assemble a multi-disciplinary team (immunologists, epidemiologists, neuropsychologists, etc.), and then examine veterans from units that had been in high-risk exposure conditions.

Dr. Cherry asked whether there was a treatment if it was determined these veterans had been infected. Dr. Magill indicated that he was not confident this would be the case, just as there was no treatment for chronic fatigue syndrome.

The meeting adjourned at 12:15 p.m. for lunch.

The meeting reconvened at 1:20 p.m.

Assessment of a role of stress-activated kinases in the pathogenesis of Gulf War Syndrome

Ya Fang Liu, MD, PhD
Department of Pharmacology, Boston University School of Medicine

Dr. Ya Fang Liu gave a presentation about the role of stress-activated kinases in the pathogenesis of Gulf War illnesses. (See Appendix A – Presentation 6.) She examined the effect of stress, vaccines and pyridostigmine bromide (PB) on stress-activated kinase activity. During her talk, Dr. Haley asked about the use of adjuvant in the vaccination in-vivo portion of her study. Dr. Liu indicated that TRH had been used. Discussion occurred about whether the tested substance was an "adjuvant" or simple protein. Dr. Liu stated that these studies were preliminary, and that the results were based upon one-year's worth of work. She stated that she hoped this study would bring some light to the research area and provide a treatment for ill Gulf War veterans.

Upon conclusion of her talk, Chairman Binns asked Dr. Liu to address possible treatment studies in light of her findings with stress-activated kinases. Dr. Liu stated that animal studies needed to be conducted, testing the effect of CEP-1347. She stated that verification, through point mutation studies, needed to be done to verify the drug's ability to inhibit stress kinase activation.

Dr. William Meggs commented that Dr. Liu's work was exciting, not only because it might lead to a treatment, but also lead to a diagnostic test. Dr. Liu stated that kinase levels could only be measure indirectly (via cytokine levels) at this time. She stated that direct kinase level tests haven't been developed yet.

Discussion occurred between Dr. Liu and Dr. Sopori about clinical trials and various levels of kinases.

Immunotoxicity of low-dose sarin and silica inhalation

Mohan Sopori, PhD
Senior Scientist and Director, Immunology Program, Lovelace Respiratory Research Institute

Dr. Mohan Sopori gave a presentation regarding his preliminary findings as to immunosuppressive effects of sarin and silica in animal (rat) studies. (See Appendix A – Presentation 7.) Dr Sopori indicated he and his colleagues had begun doing these studies in conjunction with their studies of the effects of nicotine, a cholinergic agent, on the human system. During the presentation, Dr. Haley asked as to the time frame in which sarin suppression of cortisone was observed. Dr. Sopori stated the period of time was 5 days. However, he stated his team hoped to do further experiments to determine exactly how long this suppression occurs.

Following Dr. Sopori's talk, Chairman Binns asked that discussion be postponed until the discussion period scheduled later in the afternoon.

The meeting adjourned at 3:10 p.m. for a ten-minute break.

The meeting reconvened at 3:20 p.m.

Immune dysregulation in Gulf veterans with CFS and its relationship with cognitive function and functional status

John Ottenweller, MD
Professor, Neurosciences Department, University of Medicine & Dentistry of New Jersey and
Senior member, New Jersey Environmental Hazards Research Center and War-related Illness and Injury Study Center, West Orange, NJ VA Medical Center

Dr. John Ottenweller spoke about his group's evaluation of Desert Shield/Desert Storm veterans' cytokine and cortisol levels, and their relationship to the veterans' cognitive and functional status. (See Appendix A – Presentation 8.)

Following the talk, Dr. Jack Melling asked, in light of their data, if Dr. Ottenweller thought a treatment to address the Th1/Th2 balance, was worth considering. Dr. Ottenweller indicated that it was premature to say either way at this time. He believed more study/data was needed to confirm this imbalance is occurring, and avoid possibly making that imbalance worse.

In response to Dr. Magill's concerns about sampling, Dr. Ottenweller indicated that preliminary data also showed that cortisol levels in the Desert Shield/Desert Storm veterans sampled were more variable than cytokine levels. With this higher variability, duty type (guard/reserve vs. active) became a significant factor. Those veterans who had been deployed in guard/reserve capacities had significantly lower cortisol levels seven to ten hears after deployment than the other groups. Dr. Ottenweller also noted that as veterans' fatigue levels increased, cortisol levels lowered. Dr. Haley asked if this might be age-related, considering the guard/reserve unit troops were typically older. Dr. Ottenweller stated that they had looked at this, and found no relationship between age and cortisol levels.

Dr. Golomb asked if Dr. Ottenweller's group had considered that the observed increased mRNA levels might be due to increase turnover, perhaps because of increased immune activation. Dr. Ottenweller indicated that they had, and that further study was needed to answer this question.

Dr. Melling commented that he found Dr. Ottenweller's data extremely interesting in light of a conversation with a colleague about the use of anthrax vaccine in the first Gulf conflict. His colleague had mentioned that reserve forces were targeted for anthrax vaccination because these forces were considered to be at a high risk for biological attack. His colleague indicated that the prevailing thought was the Iraqis would follow the Soviet bioweapon attack model.

Chairman Binns thanked Dr. Ottenweller.

Immune activation and Th1/Th2 cytokine balance in Gulf War-related illnesses

Mark Peakman, MBBS,BSc,PhD,FRCPath
Department of Immunology, King's College School of Medicine and Dentistry, London

Dr. Peakman spoke about his group's immunological findings, or more specifically cytokine balance findings, in ill Gulf War veterans. (See Appendix A – Presentation 9.) To better understand his power point slides, Dr. Peakman provided the following abbreviation definitions: sBEV = sick Bosnia era veterans; wGWV = well Gulf War veterans; and sGWV = sick Gulf War veterans. He also noted that the green panels indicated abnormal (or significant) findings, e.g. elevation of IL-4, IL-γ, IL-2, etc.

During the talk (at Slide 12), Dr. Haley noted that he had concerns about the GWI case definition being used in this and other studies. He noted that the case definition used was non-specific, and as such might lessen the significance of the results. He felt this was the Achilles heel of this research field. Dr. Haley enquired if they might be able to review the original Wessley data set and establish a more precise GWI case definition. Then, they could re-examine these veterans (estimated about 150). This might provide insight or generate new hypotheses, as often the outliers are the key to what is occurring. Dr. Peakman acknowledged the criticism, and noted the definition became "locked" in 1996. He stated he was struck by how their results paralleled those of Dr. Ottenweller's study, i.e., a Th2 response that was not robust, and a change in IL-10 production.

During Dr. Peakman's discussion of Slide 13, Mr. Robinson asked if Dr. Peakman's group had seen an increase in eosinophils at any stage, and if so, were the veterans who received multiple vaccines more likely to have higher levels of eosinophils. He noted that last summer; several soldiers came down with a mysterious pneumonia, and evidence of high eosinophil levels. Dr. Peakman indicated that he didn't have the data at that time.

During Dr. Peakman's discussion of Slide 39, Dr. Golomb commented that single-administration of vaccines was not typical. Dr. Peakman noted that dendritic cells don't have memory capabilities. Dr. Golomb acknowledged this, but suggested that it would be interesting to look at this in an in-vivo model to examine the expression of the different cytokines. Dr. Peakman agreed that this would be possible in a nicely controlled model.

Following the talk, Dr. Haley indicated that the most conclusive finding was with regard to IL-10 production, and wondered what it might mean. Dr. Peakman stated that he was investigating three or four possible immunological mechanisms, but needed to dissect the question more clearly with clinical studies. Dr. Haley submitted for discussion whether, in light of Dr. Sopori's animal data, there might be a primary neurological mechanism having this effect on the immune system. Dr. Peakman noted that this seemed to be related specifically to Gulf War illnesses, as it wasn't observed in chronic fatigue syndrome (CFS) patients.

Chairman Binns reopened Dr. Sopori's presentation for discussion. Dr. Haley noted that the immunologic abnormality reported by Dr. Sopori's team seemed to be associated with the sympathetic nervous system, and asked if Dr. Sopori saw a connection with IL-10. Discussion followed.

Mr. Graves asked, in light of the day's discussion about cytokines and Th1/Th2 levels, what types of treatments were available to balance these cytokines. Dr. Sopori indicated that, in asthma patients, researchers have been trying to raise Th1 levels using CpG immunization. Dr. Magill noted that IL-10 excess was a common feature in visceral leishmaniasis. As such, it was noted that a low-level/residual, undetected leishmania infection might be the cause of the reported IL-10 levels in ill Gulf War veterans. Dr. Magill noted that CpG therapies are not FDA licensed at this point, but indicated that CpG therapy for primary leishmaniasis immune therapy was being studied.

Chairman Binns asked each speaker if they would make recommendation as to what they envisioned being the most worthwhile topics to pursue in future research related to Gulf War illness.

Dr. Sopori indicated that more research was needed into whether these veterans were experiencing a subclinical/occult type of infection. Discussion occurred about leishmania rates in current deployed troops and the Iraqi population.

Dr. Liu stressed her concern that, considering the period of time since the Gulf War, treatments needed to be a focal point. She expressed excitement about the possibilities of a new Parkinson's drug in clinical trials, as well as a botanical treatment that she was researching. Dr. Golomb agreed that treatments were very important, but stated mechanism answers needed to be pursued. Dr. Golomb noted that Gulf War veterans have something different than other veterans, and the other possibilities shouldn't be discounted. Dr. Pellier expressed caution about raising veterans' hopes and making undeliverable treatment promises. He noted that there were lots of diseases, e.g., irritable bowel syndrome, stroke, etc., where little was still known. He noted that when studying a syndrome, researchers struggle to determine the underlying abnormality because of its complexity. He suggested that more symptomatic approaches might be advisable at this time, due to a lack of understanding about the syndrome's physiology.

Dr. Ottenweller expressed a concern about having baseline information (data and blood samples) for the OIF/OEF soldiers. He stated concerns had arisen in their research about whether observed/reported conditions were pre-existing or war-related. He stated that his group had tried to propose three or four blood studies, but hadn't received cooperation from DoD or VA. Mr. Robinson expressed concern about the failure to collect this information again. He indicated that many groups were asking for the data, but it was proving to be difficult. Dr. Ottenweller mentioned the January 21, 2004, OIF roster analysis, but stated it didn't contain a GWI category.

Dr. Sopori stated that the key was to figure out how the central nervous system responds in ill Gulf War veterans, and figure out why these responses trigger these types of reactions. Dr. Ottenweller indicated that his group was starting to look at this question by examining cytokine levels in CFS patient cerebral spinal fluid. Dr. Liu suggested examination of GWV brain samples might provide insight as well.
Chairman Binns thanked all of the speakers. He noted that, by seeing the complexities and differences among their hypotheses, even though inter-related, researchers could begin to fill in the pieces. He stated that, by looking at all these hypotheses together, maybe a treatment would become more evident.

Public comment – Day 1

Chairman Binns opened the floor to public comment.

Mr. Dan Fahey addressed the Committee and thanked them for reviewing the issue of depleted uranium (DU) the following day. [Copies of Mr. Fahey's written statement were distributed for the Committee's review. (See Appendix B - Public Submission 1.)] Mr. Fahey provided the Committee with an overview of problems he had found with DoD/VA study assessments of DU's effects on Gulf War veterans. He made two recommendations to the Committee: (1) the VA's DU study should be expanded to include the approximately 900 veterans identified by DoD as having Level I or II exposures during the 1991 war; and (2) due to concerns about data filtering/lack of disclosure in the current DU study, new VA program leadership enlisted to oversee the expanded study.

The meeting adjourned for the day at 6:00 p.m.

The meeting reconvened the following day, February 24, 2004, at 8:10 a.m.

Preliminary assessment of DU munitions health effects

Al Marshall
National Security Studies Department, Sandia National Laboratories

Mr. Al Marshall gave an overview of the results of the findings of his project investigating possible risks related to DU exposure, particularly in Gulf War veterans. (See Appendix A – Presentation 10.) One slide (#15) correction was noted, in that the arrow showing DU's pathway to the blood stream should have been shown from the small intestine, not the large intestine.

Following the talk, Dr. Haley asked about the amount of DU found in the brain. Mr. Marshall stated that DU definitely enters the brain through the blood and that it appears to happen rapidly. He stated that, in terms of the radiological effect, the brain was fairly insensitive. However, the chemical effect on the brain is uncertain and needs to be studied in more depth. Dr. Haley asked if there were estimates as to how much (percentage-wise) of DU went to the brain. Mr. Marshall indicated this needed to be investigated further, but he would hypothesize it to be in range similar to other soft tissue organs.

Mr. Robinson asked if Mr. Marshall thought, based on his findings, it would be a good idea to conduct a more in-depth study of the effects of DU on veterans, along with studies on the current conditions at locations involved in the first Gulf War. Mr. Marshall thought both studies needed to be conducted to put these lingering issues to rest.

Dr. Sushil Sharma, U.S. General Accounting Office (GAO), asked Mr. Marshall whether he had determined the inhalation particle size effect. Mr. Marshall stated that particle size did have an impact, but sensitivity studies still needed to be done to flesh out this concern.

Dr. Sharma asked about the extrapolation models used by Mr. Marshall. Mr. Marshall stated he used standard radiological settings, which were an extrapolation of much higher dosages. He indicated that there was considerable disagreement in the field as to what constitutes low-end exposure. Dr. Sharma asked whether Mr. Marshall had compared total DU intake vs. particle size. Mr. Marshall indicated that he had looked at these uncertainty factors.

Dr. Lewis enquired as to the solubility factors used in Mr. Marshall's calculations. Mr. Marshall stated that he hypothesized mostly U238, with some other isotopes, and had relied on tests that took the particulate amounts from various impact tests. He noted that, if one took a nominal case and predicted what amount of DU would be present in the urine seven to eight years later, he fell right on target with what was actually measured (on average). He stated that he was confident that his calculations were within a reasonable range.

An audience member inquired as to which DoD study provided the data for Mr. Marshall's calculations. Mr. Marshall stated it wasn't the "first" study, but the USACHPPM study. He stated that he had looked at all the impact data in order to make his calculations.

Chairman Binns thanked Mr. Marshall.

Overview of Armed Forces Radiobiology Research Institute Research on the effects of depleted uranium

Terry C. Pellmar, PhD
Scientific Director, Armed Forces Radiobiology Research Institute

Dr. Terry Pellmar presented an overview of the Armed Forces Radiobiology Research Institute's (AFRRI's) findings on the effects of depleted uranium. (See Appendix A – Presentation 11.) Dr. Pellmar noted that Dr. John Kalinich, her colleague, was in the audience.

During her discussion of Slide 11, Dr. Pellmar noted that, based on urine data comparisons, a four-pellet DU dosage in the rats was comparable to the highest level of Gulf War veterans' exposure. She also noted that a steady state in urine and kidney DU levels was reached after six months. However, the DU levels in bone continued to increase throughout the life of the animal. As the rats continued to grow and experience bone elongation, she wasn't sure how this would translate into adult humans.

With respect to kidney function, Dr. Pellmar stated that they found no evidence that DU adversely affected the kidney. She stated that this wasn't what they expected, and that a possible explanation might be enzyme up-regulation or perhaps the DU was being sequestered in some manner.

Dr. Liu and Dr. Melling questioned the animal (rat) model chosen without knowledge of the toxicological mechanisms. Dr. Pellmar indicated that, based on their findings' correlation with Dr. McDiarmid's Gulf War veteran findings, they were confident about their choice of model organism.

Following the talk, Dr. Pellier asked whether AFRRI had studied the effect of the pellet shape on DU uptake. He noted that pellets with higher surface area might result in higher exposures. Dr. Pellmar stated they hadn't performed this study, because of the difficulties in maintaining controls. However, she noted that, while the pellets were originally smooth, the evidence showed the pellets began to disintegrate quickly, increasing the overall surface area.

Dr. Haley questioned the focus on LD50 dose effects, rather than individual dose effects. He stated it would be interesting to look at the variable results in individual animals because there was indication that there could be increased individual susceptibility. Dr. Pellmar found this to be an interesting point, but noted it wasn't clear with these findings whether the variances were due to animal or measurement issues. She stated extra/multiple replicates were necessary to say definitely it was an animal variability issue. Dr. Haley referenced a previous study, involving marmosets and sarin that used this approach.

Dr. Haley asked how long did they (Dr. Pellmar's group) expect uranium to be excreted in humans. Dr. Pellmar stated that the studies hadn't been done, but she expected DU would be excreted until the pellet's reservoir was depleted.

Dr. Sharma (GAO) asked about the results of DU/sarin experiments. Dr. Pellmar stated that AFRRI hasn't worked with sarin.

Mr. Steve Smithson asked what happened to fragments in Gulf War veterans. Dr. Pellmar stated it was difficult to say, but she expected the pellets to be acting as a DU reservoir. Dr. Steele asked, if this was the case and based upon their mutagen and transformation findings, could there be reason to recommend removal of the DU fragments from the veterans. Dr. Pellmar stated, in her personal opinion, unless major problems with a particular fragment arose, the fragment should be left alone. Dr. Pellier questioned this position, because her data showed DU had mutagenic effects and they hadn't established a "no effect" level. Dr. Pellmar stated that the basis for her opinion was the lack of change in the rats' lifestyle and cancer rates. Colonel Jarrett, director of AFRII's laboratory and an Army emergency room surgeon, was in the audience and concurred with Dr. Pellmar's position. He stated that the current protocol was to take out easily accessible fragments, but leave in fragments when the removal process would cause extensive damage.

An audience member asked whether bacterial films had been observed surrounding the transformed cells. Dr. Pellmar stated that bacteria weren't observed, but fibrous tissue had been.

Mr. Robinson inquired whether AFRRI had conducted any tests in Iraq or other places where troops might have been exposed to DU. Colonel Jarrett stated that this type of study was not in AFRRI's mission. He noted that when they did venture into DU research, they were stepping somewhat outside their range. Dr. Pellmar also noted that AFRRI's mission was to do basic, not clinical, research.

Mr. Dan Fahey asked whether time frame matching had been considered between the rat model and Gulf War veteran data. Dr. Pellmar noted two things she felt addressed this concern: (1) the DU animal group's levels were equivalent to the highest-level seen in veterans; and (2) the animal model's DU excretion levels leveled off (became steady) after six months.

Chairman Binns thanked Dr. Pellmar.

The meeting adjourned at 10:00 a.m. for a break.

The meeting reconvened at 10:15 a.m.

Inhalation of uranium oxides to mimic Gulf War exposures: Deposition and toxicity in brain, lung, and kidney

Johnnye Lewis, PhD, DABT
Director, Community Environmental Health Program, University of New Mexico Health Sciences Center

Dr. Johnnye Lewis provided the Committee with background as to how her team was investigating the inhalation of uranium aerosols, and addressed their early findings. (See Appendix A – Presentation 12.)

Following the talk, Dr. Golomb asked if Dr. Lewis had considered a correlation between this research and reported symptoms of MCS patients exposed to pesticides. Dr. Golomb noted that affected female-to-

male ratios were high in MCS too. Dr. Lewis indicated that obtaining tissue samples would be relatively easy, but deciding how to test would be harder.

Dr. Haley enquired as to the high mortality rate in the study's female rats. Dr. Lewis stated that this was not an anticipated result, and they were not sure what the possible reasons were.

Dr. Haley asked if it was known how long the DU aerosol spray stays suspended in the air. Dr. Lewis indicated that this had been a consideration in their study. She stated that there was data in the literature on this, and noted that the time was dependent on the size of particles generated.

Mr. Graves asked whether the solvents, e.g., oil from fires, in the atmosphere might have increased a soldier's DU uptake. Dr. Lewis stated that they were beginning to characterize some of these particulate distributions.

Chairman Binns thanked Dr. Lewis.

Health effects of depleted uranium in exposed Gulf War veterans – A ten-year follow-up

Melissa McDiarmid, MD, MPH
Director, Depleted Uranium Program, Baltimore VA Medical Center

Dr. Melissa McDiarmid presented an overview of VA's DU surveillance program, along with data (including the most recently published 2001 data) collected from veterans involved in friendly fire incidents. (See Appendix A – Presentation 13.)

Towards the beginning of Dr. McDiarmid's talk, Mr. Anthony Principi, Secretary of the Department of Veterans Affairs, arrived. Dr. McDiarmid graciously yielded the floor to Secretary Principi. Secretary Principi apologized for the interruption, and stated he just wanted to stop by and thank Chairman Binns and the rest of the Committee for their hard work and effort to find conclusions to the health issues that Gulf War veterans have been grappling with for a long time. He indicated that he had been spending a lot of time with returning OIF soldiers at Water Reed and Bethesda hospitals. While many of these soldiers' injuries involve shrapnel, he stated that there are many environmental hazards on this war's battlefield, as there was in the first Gulf War. For this reason, he stated that the Committee's work was very important in identifying the issues, as well as the research to answer these concerns. He stated that there simply was no more urgent mission than to find answers for the men and women who commit themselves on the battlefield and to help devise ways to protect our troops. He stated that he was committed to this Committee's effort.

Dr. McDiarmid returned to her talk, explaining the surveillance protocol for her group's study. During her discussion of the 2001 cohort renal function findings, she also discussed the urinary markers for toxic nephropathies identified in the European Cooperative Study. Mr. Graves asked whether there was a correlation between the lead/heavy metal data and emerging DU data. Dr. McDiarmid stated that, in terms of prognosis and the hierarchy of heavy metal renal insults, uranium would be towards the bottom of the list. Mr. Graves asked if there was any form of treatment, e.g. detoxification. Dr. McDiarmid stated there wasn't.

Towards the end of her talk, Dr. McDiarmid provided an overview of the VA's nation-wide uranium sampling program. She described the process by which veterans mail in urine samples for testing. She presented data from 446 GWV (three of which were in the original cohort of friendly-fire veterans) and 147 OIF veterans (Air Force and Marines). Their preliminary findings indicated that these veterans'

creatinine levels were within appropriate ranges. Mr. Smithson asked if any of the OIF veterans retained shell fragments. Dr. McDiarmid indicated that this data was coming to them in pieces at this time, due to problems with centralizing communication between VA and the armed forces branches. She indicated that, based upon this data, she believed there wouldn't be a health risk problem associated with DU in the future.

Chairman Binns thanked Dr. McDiarmid. He apologized to the Committee and audience for the lack of flexibility in the meeting's time schedule for a formal discussion/question period. Dr. McDiarmid offered to stay and answer individual questions privately.

The meeting adjourned at 12:07 p.m. for lunch.

The meeting reconvened at 1:07 p.m.

Committee Business

Chairman Binns asked the Committee to take time at that point for discussion, specifically as to their reactions to the VA funding status report heard the previous morning. Chairman Binns stated that he had hoped to have this discussion before meeting with Secretary Principi. However, their meeting had been rescheduled, and he had just come from the Secretary's office. He stated that he presented some ideas expressed to him by Committee members the previous day.

The Committee discussed their concern about the lack of GWI-related studies funded by VA. They expressed concern that this research had been "disguised" under the deployment health initiative and had likely not interested field researchers, and had not been reviewed by peer-review panels that had special knowledge about GWI. Dr. Haley spoke about the Juvenile Diabetes and NIH AIDS vaccine research funding projects. He indicated that both groups had spent time reviewing the current research and tailored funding announcements to invite numerous, exciting proposals. Dr. Melling noted that a focus strategy was needed when developing funding announcements. Otherwise, the approach will diffuse the resulting pool of proposal applications.

Mr. Graves stated that, in his opinion, VA ORD hadn't spent any money on GWI, but believed there was still a chance this year for the Committee to get involved and change things. Dr. Golomb suggested the funding announcement list the types of research that were important for breakthroughs, e.g. treatment, acetylcholinesterase, etc., but also indicate a non-interest in proposals that focus on stress/psychological research. Dr. Melling suggested that, at the next Committee meeting, there be a short session to discuss what research models succeeded, and why they were able to accomplish what they did.

Chairman Binns pointed out that time was of the essence, both with the end of the fiscal year approaching and possible administration changes later in the year. He stressed that this was an urgent problem. He suggested that the Committee provide VA ORD with needed expertise in this area. He found urgency, earmarked funds, and a special Gulf War review panel to be the ingredients that would turn things around. He noted that VA had the Committee's initial recommendations, and needed to push forward. Discussion occurred about the need to encourage collaborations with outside (non-VA) researchers. The Committee discussed how this would help widen the research pool, as well as knowledge/ideas.

Chairman Binns stated he was pleased with this discussion. He stated that he was able to offer positive ideas to the Secretary, while getting across displeasure at the way the current DHI announcement was

handled. Chairman Binns stated that all of the parties want to address GWI concerns, and the key was working together to address these concerns.

Discussion occurred about the VA field researchers' disillusionment with submitting proposals in this area of research. Chairman Binns noted the dichotomy between the Committee hearing every meeting from scientists doing exciting work, but that when VA funding doors were opened, nobody came forward.

Overview of Research on Infectious Diseases in Gulf War veterans

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

Dr. Steele provided a brief overview of GW-related infectious disease research being done. (See Appendix A – Presentation 14.) Most of this research has focused on leishmania and mycoplasma infections.

Antibiotic Treatment of Gulf War Veterans' illnesses

Sam Donta, MD
Retired Professor of Medicine, Boston University School of Medicine

Dr. Sam Donta, as principal investigator (PI) on the VA's antibiotic treatment trial on Gulf War veterans, provided an overview of the study's results, as well as his insights into the study's development, design and technical issues. (See Appendix A – Presentation 15.)

Dr. Donta noted that this study was initiated, in part, in response to Congressional concerns about Dr. Garth Nicolson's mycoplasma findings. Dr. Donta stated that he was asked to be on the study's committee, because he had been a PI on a couple of other infectious disease studies, and also because of his work in Lyme disease. He stated that he hoped the scientific community now was in agreement that the Gulf war veterans were really sick, by any parameter.

Dr. Donta provided a history of the development of the study's design. At first, the researchers thought they might combine the antibiotic and cognitive behavior therapy (CBT) trials. But ultimately, this was rejected. The results of the CBT trial (published in JAMA) showed initial improvement in the Gulf War veterans' health. Dr. Donta noted that there was concern about the basis for the initial study hypothesis but that subsequent studies had provided support for the hypothesis.

Dr. Donta stated that the focus on the cause of GWI might be too narrow. He noted that the focus had been that these veterans were in the Gulf War, and therefore they "got" something from the Gulf War. He acknowledged this is possible, but suggested that it also could be a reactivation of a previously latent process, one which is reactivated by stress. He noted that the fibromyalgia, chronic fatigue syndrome and Lyme disease literatures were filled with cases where people were asymptomatic, and after going through a stressful process, reactivated a latent disease. He stressed that there could be several causes behind GWI. He noted that chemical assaults should reach some stable level of damage. He noted, however, that an individual may have a chronic underlying infection, but see fluctuations in his or her symptoms.

Dr. Donta discussed the problems with specimen handling/processing. He also discussed why doxycycline was chosen as the study's antibiotic. He stated that his clinical experience indicated doxycycline might not work because it was highly protein bound. He had suggested tetracycline, while

various drug companies promoted the use of their respective antibiotics. He stated that doxycycline was finally selected, in part due to Dr. Nicolson's strong belief in its effectiveness.

Dr. Donta addressed the study's length of time, i.e. 12 months. He stated it was in part to deter criticism that the treatment hadn't been administered long enough. However, he noted that the period time also draw criticism that it was too long, in light of current antibiotics protocols.

During his discussion of the study's exclusion criteria (Slide 6), Dr. Donta stated that it is difficult to identify these types of intracellular infections. He indicated that there was a need for a tissue registry to improve understanding in this field.

During his discussion of the study's results (at Slide 13), Dr. Donta discussed criticisms raised about the study's control groups. He stated that they had considered using an additional control group of well, non-deployed Gulf War era veterans. However, he stated this had been rejected due to the concern of making the study too large. The study researchers' consensus was that they could control within the ill group appropriately (treatment vs. non-treatment). Dr. Donta noted that they had also considered providing treatment to PCR negative (-) mycoplasma patients. He stated that these were broad-spectrum antibiotics, and it might provide a clue to helping this patient group although he noted that duration of treatment would be a major concern.

Dr. Donta stated that adverse effects to the doxycycline were relatively few. He noted that nausea was more prevalent in the group receiving doxycycline, but, interestingly, myalgia symptoms were reported less than in the placebo group.

During his discussion of mycoplasma conversion rates (Slide 18), Dr. Donta acknowledged that the biggest conundrum was finding that a majority of both groups (doxycycline and placebo) had converted to mycoplasma negative (-) within eighteen months. He stated that additional study was needed to address quality control questions. He noted that the opportunity for PCR contamination was enormous. Discussion occurred about false negatives. Dr. Golomb noted that these results would suggest that less contamination occurred over time.

Dr. Donta noted that his group had looked for three mycoplasma subsets or species (*M. fermentans*, *M. genitalium*, *M. pneumoniae*). *M. pneumonia* proved to be the control species (no more than 5% of the ill Gulf War veterans evidenced this). *M. fermentans* and *M. genitalium* were present in more veterans, overwhelming so, which correlated with the study's hypothesis. Dr. Donta stated his belief that these test results were limited, due to the low levels detected. He did acknowledge, that repeat testing could be a problem too. As far as the mycoplasma subsets, he stated there wasn't enough data to show the variation between *M. fermentans* and *M. genitalium*. But the number of *M. pneumonia* didn't change.

Similarly, Dr. Donta stated there weren't enough data when they looked at doxycycline levels to provide statistical significance. He stated this needed to be fleshed out in further papers. When questioned if the patients were consistent in taking the doxycycline, Dr. Donta indicated he believed so. He noted that doxycycline had a long half-life, and if it was in the patient's system, they should have detected it even after several days.

Dr. Donta ended his presentation with two thoughts: (1) Even if a treatment study doesn't work, researchers still need to keep looking for the cause, including infectious agent causes. He stressed the need to look at low-level infection types, citing leishmania; and (2) the need to continue searching for treatment options. He suggested three/four month trials might be something to consider. This would provide a quick idea as to whether a treatment hypothesis has possibilities.

Following the presentation, Dr. Haley asked if serology was a reasonable marker of having been in contact with the organism. Dr. Donta stated that if one has an antibody to a particular organism, they would have been in contact. Dr. Golomb commented, though, that false negative (-) results with mycoplasma were common. Dr. Donta agreed; being sero-negative doesn't preclude previous contact.

Dr. Donta stated that mycoplasma, as a cause of GWI, could not be discounted totally by this study. Methodology issues needed to be addressed.

Chairman Binns asked if Dr. Donta, himself, had tried tetracycline treatment on ill Gulf War veterans. Dr. Donta indicated that he had, though not enough to constitute a study. Based on his observations, the veterans improved more on tetracycline than doxycycline, but the overall success rate still wasn't that good.

Dr. Donta stated that a pilot or smaller treatment studies needed to be done. He indicated his willingness to help design these studies. He suggested they be over a 20-week period with 20 patients in each group. He noted that the results might not help the first Gulf War veterans, but may help those returning from the current war. Dr. Donta also stressed the need to improve investigative tools to address concerns about processes, e.g., freezing/thawing of whole blood samples, might adversely affect the results.

Dr. Meggs asked if researchers needed to look at the idea of multi-stressors, i.e., if the person was "damaged" in some way, this might be compounded by their response to stress. Dr. Donta agreed that stresses do contribute to morbidity. Whether they help reactivate the genes was a question though. He indicated that he thought it was possible based upon his clinical experiences. He noted that biochemically it would be difficult to decipher.

Dr. Steele asked if Dr. Donta, in his clinical practice, had observed Gulf War veterans being more resistant to antibiotic treatment than Lyme disease patients. Dr. Donta stated the opposite was true; the Lyme patients who had been sick for more than 4 or 5 years were more resistant. He believed that duration of illness was the key. Dr. Steele asked if the reported improvements were sustained following treatment. Dr. Donta indicated yes. Dr. Steele also asked if there was a patient subset that improved substantially, which Dr. Donta affirmed. Dr. Golomb asked if some of the veterans, even those within the significant improvement group, experienced relapses later. Dr. Donta stated that some do. Dr. Golomb noted that this was compatible with the idea of another underlying factor. She stated that the infection added an additional detrimental function, but antibiotic treatment would only reverse the infection, not all factors.

Dr. Quentin Demming, who was in the audience, commented that, from his experience, it was possible that the study showed a successful suppression of a microbial disease.

Chairman Binns thanked Dr. Donta.

Review of recent (and recently identified) Gulf War research

Beatrice Golomb, MD, PhD
Asst. Professor, University of California at San Diego School of Medicine

Dr. Beatrice Golomb gave a brief review of recent Gulf War research, including discussion about the findings of the 2003 Australian Health Study and various other studies. (See Appendix A – Presentation 16.)

Committee Business

Dr. Steele commented that she was working on drafting the 2004 Committee report. She apologized for the lateness, indicating that it was larger than anticipated. She stated that she hoped to have a draft for circulation within the next month or so.

Dr. Steele also noted that the draft letter to the editors of *Military Medicine* was still pending. She reminded the Committee members to send her their comments, even if it was a just a confirmation of approval, as all Committee member names would be on the article.

Dr. Steele asked for the Committee's feedback on the format of the monthly update from Committee staff. The consensus was that they liked it. Dr. Steele noted that committee members were welcome to send news and research articles for inclusion in the update. She stated that the attachment size may be a problem for some members, and offered to send only abstracts if a member preferred. She mentioned that staff was working on website options. She also noted that the Committee's growing research library was probably one of the best anywhere. She stated that if a Committee member needed an article, they should feel free to contact staff.

Dr. Steele noted that the Committee had a new e-mail address for public inquiries and submissions: RAC@med.va.gov.

Chairman Binns asked whether the Committee's updates could be made available to the public. Dr. Steele and Ms. Palmer indicated that they were investigating this possibility.

An audience member asked about the availability of the presenters' slides. Dr. Steele stated that the slides would be available in the minutes. She noted that some might be slightly modified by the presenter if a slide contained unpublished data.

Chairman Binns commented that the meeting had been of high caliber. He noted that Dr. Steele already was working on the upcoming meeting's schedule. He stated that with all the knowledge out there, he believed that things would gradually start to piece together. However, he also welcomed Dr. Donta's comment that treatments shouldn't wait until the whole puzzle has been deciphered.

Public comment – Day 2

Ms. Venus-valiery Hammack, Army Retired, stated that she had prepared her comments in writing. However, she indicated that she needed to amend them and would provide them at a later date. She noted that the Committee had covered her issues about the implementation and follow-up on the Committee's previous recommendations to VA.

Dr. Steele noted that the Committee was inviting people to supplement their oral testimony with written two-page (or less) statements/summaries.

Next, Ms. Denise Nichols addressed the Committee with her concerns about GWI research. She also provided the Committee with a two-page written comment. (See Appendix B – Presentation 2.) She stated that administrators/researchers needed to do a computer match-up, by Social Security number, to have a more accurate number of deaths. She stated her belief that there were more Gulf War veteran deaths than those being counted. Dr. Steele stated that the GWVIS report did report only total numbers,

but the on-going epidemiological studies did do matches using Social Security numbers. Ms. Nichols thanked Dr. Steele for the clarification.

Ms. Nichols informed the Committee about the recent death of a Gulf War veteran, who was a part of Dr. Haley's neurological study group. She suggested establishment of a mortality review committee, similar to those found in hospitals. She stated that this type of review might provide missing clues to why Gulf War veterans are sick. She suggested more research into the triglyceride/cholesterol levels of Gulf War veterans. She also stated that many have very high levels, and several are dying of sudden heart attacks. She asked whether this might be due to an early aging factor. She stressed the need to investigate new paths in this area of research.

Ms. Nichols stated that the quality of VA care for Gulf War veterans was very low. She stated the lack of care created frustrations for the ill veterans. She suggested making a panel to review the quality of care for Gulf War veterans. She stated that she was working with veterans to gain better access to healthcare and VA benefits. She stated that their military administration folders were missing important documents, causing the veterans many problems, including denied claims.

Ms. Nichols suggested that more research be done on Gulf War veterans' magnesium levels. She noted similar problems in CFS patients and individuals who had undergone radiation therapy. She suggested going back and looking at old radiation studies for clues.

Ms. Nichols noted her appreciation for the Committee's efforts. She stated that the Committee was working hard and trying to make process, but outside influences hadn't helped it along. She stated that she had enjoyed the meeting's presentations.

Chairman Binns thanked Dr. Steele for coordinating the meeting presentations. He then asked if there were any final comments or questions.

Mr. Robinson stated that he, along with some others, had a conversation with Dr. McDiarmid following her presentation. He stated that they had wished to discuss some outstanding issues regarding the VA's DU program. He indicated that she had not been open to discussing some of their questions. He asked if the Committee could send her a list of follow-up questions and request written responses. Chairman Binns indicated that this was possible. He stated that Committee members could send questions to the Committee's staff and then circulate the final list before submitting it to Dr. McDiarmid. Dr. Steele also indicated that Dr. McDiarmid could be invited back to a later meeting.

Chairman Binns thanked the Committee for its hard work, and noted the members' outstanding attendance record.

The meeting adjourned at 3:27 p.m.