Research Advisory Committee on Gulf War Veterans' Illnesses

June 28-29, 2004 Committee Meeting Minutes

U.S. Department of Veterans Affairs
East Orange, NJ, War-Related Illness and Injury Study Center (WRIISC)
385 Tremont Ave.
East Orange, NJ

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 June 28-29, 2004, meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses.

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

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Attendance Record

Members of the Committee 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
Kevin Beck
Helena Chandler
Don Ciccone
Dane Cook
John Concato
Liesel Copeland
Allen Fienberg
Tom Findley
Paul Greengard
Drew Helmer
Roger Kaplan
Gudrun Lange
Sharon Mates
Benjamin Natelson
John Ottenweller
Karen Quigley

Abbreviations

AChE	Acetylcholinesterase
ALS	Amyotrophic Lateral Sclerosis
BuChE	Butyrylcholinesterase
CBT	Cognitive Behavioral Therapy
CDC	Centers for Disease Control
CRADO	Chief Research and Development Officer (VA)
DOD	U.S. Department of Defense
HRQ	Agency for Healthcare Research and Quality
IBS	Irritable Bowel Syndrome
IT	Intracellular Therapies, Inc.
NCCAM	National Center for Complementary and Alternative Medicine (NIH)
NIH	National Institutes of Health
NINDS	National Institute of Neurological Disorders and Stroke
OEF	Operation Enduring Freedom
OIF	Operation Iraqi Freedom
ORD	Office of Research and Development (VA)
PB	Pyridostigmine Bromide
PON1	Paraoxonase
PTSD	Posttraumatic Stress Disorder
REAP	Research Enhancement Award Program
RFA	Request for Applications
RFP	Request for Proposals
VA	U.S. Department of Veterans Affairs
VACO	U.S. Department of Veterans Affairs Central Office
VSO	Veteran Service Organization
WRIISC	War-Related Illness and Injury Study Center

Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses
East Orange Campus of the VA New Jersey Health Care System
1st Floor Museum, 385 Tremont Avenue East Orange, New Jersey

Meeting Agenda

Monday, June 28, 2004

8:30	Welcome, introductions, and opening remarks	Jim Binns	
8:40	Welcome	Dr. Benjamin Natelson	
8:45-9:15	Overview of NJ CFS research	Dr. Benjamin Natelson	
9:15-9:45	Overview of NJ Environmental Hazards Center research on Gulf veterans	Dr. Tom Findley	
9:45-9:50	WRIISC Center Mission	Dr. Benjamin Natelson	
9:50-10:30	WRIISC Research I: Overview of completed and pilot studies	Dr. John Ottenweller Dr. Dane Cook	
10:30–10:45	Break		
10:45-12:00	WRIISC Research II: Ongoing studies	Dr. Servatius Dr. Natelson Dr. Quigley Dr. Copeland	Dr. Helmer Dr. Findley Dr. Santos
12:00-1:00	Lunch		
1:00-1:30	WRIISC Research III: New research	Dr. Quigley Dr. Cook	Dr. Chandler Dr. Natelson
1:30-2:00	WRIISC Research IV: Planned studies	Dr. Ottenweller Dr. Ciccone Dr. Findley	Dr. Quigley Dr. Helmer Dr. Copeland
2:00-2:10	Deployment REAP (Research Enhancement Award Program)	Dr. John Ottenweller	
2:10-2:30	Discussion of areas where future research is needed	Dr. John Ottenweller WRIISC group	
2:30-2:45	Break		
2:45-2:50	Review of WRIISC Clinical/Education/Risk Communication Missions	Dr. Benjamin Natelson	
2:50-3:00	Veterans seen in WRIISC Center	Dr. Drew Helmer	
3:00-3:15	Clinical evaluation of Gulf War and OEF/OIF veterans	Dr. Ronald Teichman	
3:15-4:30	Overview and discussion of treatments for unexplained illnesses	Dr. Benjamin Natelson WRIISC group	
4:30-5:15	Tour of WRIISC facility	Dr. John Ottenweller	
5:15-5:30	Public comment period		
5:30	Adjourn for the day		

Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses
East Orange Campus of the VA New Jersey Health Care System
Room 11-137 385 Tremont Avenue East Orange, New Jersey

Meeting Agenda

Tuesday, June 29, 2004

8:30-9:15	Update on VA ORD Gulf War illness research initiatives and activities	Roger Kaplan
9:15-10:00	Update on study of AChE-R in Gulf War veterans	Dr. John Concato
10:00-10:15	Break	
10:15-11:00	Recent research update	Dr. Beatrice Golomb
11:00-12:00	Research Concept: Understanding the Biochemical Basis of Gulf War Illnesses	Dr. Paul Greengard Dr. Sharon Mates Dr. Allen Fienberg
12:00-1:00	Lunch	
1:00-2:00	2004 Report, Committee business	Jim Binns Dr. Lea Steele
2:00-2:30	Public comment period	
2:30	Adjourn	

Welcome, introductions, and opening remarks

Mr. James H. Binns, Jr., Chairman

Chairman James Binns called the meeting to order at 8:28 a.m.

Chairman Binns introduced Dr. Paul Greengard, PhD, Nobel Prize laureate (2000), who holds the Vincent Astor professorship at Rockefeller University and heads its Laboratory of Molecular and Cellular Neuroscience. Chairman Binns noted that Dr. Greengard's research had helped uncover the molecular mechanisms involved in Parkinson's disease, which lead to the disease's standard treatment today. Chairman Binns stated that he had met Dr. Greengard at a Spring, 2004, conference sponsored by the National Institutes of Health's National Institute of Neurological Disorders and Stroke (NINDS). He had been very excited to learn of Dr. Greengard's recent research, which included work with the Army Chemical Defense Institute. Chairman Binns stated that he was delighted that Dr. Greengard, with his neuroscience expertise and knowledge of Gulf War illness, wished to conduct future research into Gulf War illness. Chairman Binns noted that Dr. Greengard had already made a major contribution to the field of Gulf War illness research just by his interest and acknowledgement of the field.

Dr. Paul Greengard thanked Chairman Binns and described him as a hero in this field himself for bringing this issue to the forefront. Dr. Greengard stated that the Committee's work was remarkable, and felt a debt of gratitude was owed to all.

Dr. Greengard provided a short review of his research into the understanding of the chemical mechanisms that allow brain nerve cells to communicate with each other. While these chemical pathways were complex and had numerous steps, he stated that knowing more details about this "machinery" provided more opportunities for therapeutic interventions. He listed three steps in understanding these pathways: (1) determining how nerve cells communicate with each other; (2) determining how to use this information to better understand the nature of various neurological and psychiatric disorders; and (3) determining how to use this information to better understand the mechanism by which to treat neurological and psychiatric disorders.

Dr. Greengard stated that his previous Parkinson's disease research ran parallel with Gulf War illness, and this is why he found it to be an intriguing and challenging field. He stated that, being new to this field; he was amazed at the reactions among many government constituencies with regard to Gulf War illness. He was surprised that it seemed that so many people thought Gulf War illness was a way for veterans to "rip-off" the government. Based on their accounts, he found it remarkable that a large group of veterans would be reporting similar symptoms unless there was some real conspiracy.

Dr. Greengard said there was overwhelming evidence that Gulf War illness wasn't due to stress, but that some particular factor or factors in the environment was responsible for the symptoms of ill Gulf War veterans. From his knowledge of the literature, he stated that the leading candidates were several compounds used in the field that inhibited cholinesterase, e.g., nerve agents, pesticides, pyridostigmine bromide (PB), etc. He explained that all of these compounds work by the same mechanism. He also discussed the company (Intracellular Therapies, Inc.) that he co-founded with Dr. Sharon Mates and Dr. Allen Fienberg. He stated that one of their major focuses of interest was determining how chemical warfare agents achieve their effect. He said that this interest came about because there was a higher incident of Parkinson's disease in soldiers. He stated that research into Gulf War illness seemed to be a natural expansion of his work.

Dr. Robert Haley asked Dr. Greengard if he could speculate on what we were likely to find about the mechanism of this illness, and whether it was likely the effects could be reversed. Dr. Greengard stated

that a hopeless recovery scenario would be one where the nerve cells had died. He stated, that from the best of his knowledge, there wasn't evidence that this was occurring in Gulf War veterans. Thus, he was optimistic about treatment options. He stated there were at least 17 different targets (12 nicotinic and 5 muscarinic) for acetylcholinesterase. Nerve agents maintain a high level of acetylcholine by inactivation of these targets, which can cause changes in the levels of the targets. He noted that there were many consequences due to changes in receptor activation. He stated that better drugs could be developed that would prevent this activation. He noted that PB basically blocks all acetylcholine activity to all parts of the brain. He stated that he was very optimistic that researchers would be able to determine which pathways are most affected by nerve agents, and discover selective antagonists for each pathway to protect military and civilians exposed to chemical warfare or terrorism. He stated that he also was optimistic, though somewhat less, that medications could be developed which would reverse changes if given within short periods after such an attack. As for Gulf War illness treatments, or the possibility of reversing changes that occurred fourteen years ago, he indicated that there was a possibility that a compound could be found that corrected the changes in the brain's chemical signals. He acknowledged that his optimism wasn't as high as for the other two scenarios, but he thought it very logical and saw no reason not to investigate the possibility more.

Ms. Marguerite Knox asked Dr. Greengard if he thought some Gulf War veterans were more sensitive to low-level chemicals, and if so, did he think that genetic testing could be developed that would identify these individuals so more preventive actions can be taken. Dr. Greengard stated that there were probably both genetic and environmental exposure components to Gulf War illness. He stated that research should be done to see which of the 17 different acetylcholine receptors was the most sensitive. With this knowledge, he said that genetic analyses could be conducted to study the composition of these 17 receptors within different Gulf War veteran populations, and whether there was a correlation between those with the most severe illness and the levels of these 17 compounds. He noted that the possibilities weren't limited to these 17 compounds, but that there were a minimum of 10 other steps, resulting in 170 avenues that would need to be examined.

Mr. Joel Graves asked Dr. Greengard what his personal research plans were in this area. Dr. Greengard stated that the work could be done through his company, Intracellular Therapies, Inc. (IT). He stated that the basic biology of the acetylcholine pathways would be studied at Rockefeller University, but IT would be taking this information and begin screening potential chemical treatment compounds. He stated that Dr. Fienberg would present more details about this research during the next day's meeting.

Chairman Binns thanked Dr. Greengard.

Development of the East Orange, NJ, WRIISC center and Overview of Local Research Regarding Chronic Fatigue/Fibromyalgia in Civilians

Dr. Benjamin H. Natelson, MD
Executive Director, East Orange, NJ, War-Related Illness and Injury Study Center (WRIISC)

Chairman Binns introduced Dr. Natelson, Executive Director of the East Orange, NJ, War-Related Illness and Injury Study Center (WRIISC), and Professor of Neurosciences at the New Jersey Medical School.

Dr. Natelson introduced the WRIISC's section directors: John Ottenweller, Tom Findley, Ron Teichman, and Gudrun Lange. He stated that the WRIISC had just received confirmation that it would have a post-doctoral training program in war-related illness. He said that two positions had been created in this program.

Dr. Natelson presented an overview of the development of the WRIISC and an overview of current research, including his own, into chronic fatigue syndrome in civilians. (See Appendix A – Presentation 1.)

Following Dr. Natelson's presentation, Mr. Steve Robinson inquired about the number of Gulf War veterans seen at the WRIISC since its establishment. Dr. Natelson stated that a "guestimate" would be about 100. Mr. Robinson asked Dr. Natelson to expand on his comments about having no mechanism for veteran travel to the WRIISC. Dr. Natelson stated there was a mechanism, but that it required the NJ VA to pay for the veterans' travel, at least one-way. Mr. Robinson stated that Dr. Mark Brown at the Department of Veterans Affairs' Central Office (VACO) had indicated to him that any veteran could come to the WRIISC and that the burden wasn't put onto the hospital. Mr. Robinson stated there seemed to be a disconnect between these two understandings of the travel process. Dr. Natelson stated that his understanding was the veteran's local VA paid the travel one-way, while the NJ VA paid the travel the other way. This, he noted, resulted in the NJ VA paying 50% of all travel to the WRIISC. He stated that because of this the WRIISC was concentrating on recruiting veterans within 75 miles of the East Orange, NJ, facility.

Mr. Robinson asked about the WRIISC's problems finding healthy controls from the Iraq and Afghanistan conflicts. Dr. Natelson noted there was a real problem finding healthy controls from the first Gulf War. Mr. Robinson stated that, as he understood, the VA didn't collect a history of where veterans served, including possible environmental exposures/hazards that the veteran might have experienced. He stated that he didn't understand the logic of this, and then asked if the East Orange, NJ, VA hospital tried to collect this data. Dr. Natelson said that the veterans seen at the WRIISC were asked questions about collective exposures.

Mr. Steve Smithson suggested that the WRIISC contact veteran service organizations (VSOs), e.g., American Legion and Veterans of Foreign Wars, to get the word out to their members about the need for healthy controls. Dr. Natelson said that the WRIISC had done this on a local level. He stated that without the VSOs' help the WRIISC researchers would be in real trouble. He noted that having a database of willing healthy controls would be really helpful.

Dr. Golomb commented that she didn't believe it was yet time to have the WRIISC's four focus areas (research/clinical/education/risk communication) considered equally important. She stated that more information was needed to provide education scenarios. Dr. Natelson agreed, but stated that this was the directive from VACO. He noted that there could be efforts to communicate the message that Gulf War illness was a real, organic problem with risks. Dr. Golomb concurred that previous VA physician training had taught that there wasn't really anything significant organically wrong with Gulf War veterans, and wondered if there were efforts to correct this. While not part of the WRIISC's current vision, Dr. Natelson stated that they were trying to do this at a local level, at least with senior management level staff. He stated that the WRIISC didn't have the resources to address this issue on a larger level.

Dr. Haley commented that he found Dr. Natelson's idea about risk communication very interesting. He stated that he had seen risk communication between VA/Department of Defense (DOD) and the patient used as propaganda to convince the patient that they weren't ill, but hadn't thought about risk communication between the WRIISC and VA physicians. Dr. Haley asked if the WRIISC was internally educating the East Orange, NJ, VA physicians. Dr. Natelson stated that Dr. Drew Helmer was working on this front. Along with being the WRIISC's clinical director, he is a primary care doctor at the VA, and is currently the local Gulf War Registry physician.

Overview of New Jersey Environmental Hazards Center's Gulf War veterans research

Dr. Tom Findley, MD, PhD
Associate Research Director, East Orange, NJ, WRIISC

Dr. Findley presented an overview of the Gulf War-related research conducted earlier at the East Orange, NJ, Environmental Hazards Center. (See Appendix A – Presentation 2.)

Following Dr. Findley's presentation, Dr. Lea Steele noted that the published studies reviewed by Dr. Findley were included in the Committee's meeting notebooks.

Chairman Binns thanked Dr. Findley.

WRIISC Research I: Overview of Completed and Pilot Studies

Dr. Dane Cook, PhD
Dr. John Ottenweller, PhD
Dr. H. Liesel Copeland, PhD

Dr. Natelson introduced Dr. Dane Cook, who was one of the WRIISC's researchers. Dr. Cook gave a presentation entitled, "Pain Sensitivity in Gulf Veterans with Medically Unexplained Musculoskeletal Pain." (See Appendix A – Presentation 3.)

Following the presentation, Dr Pierre Pellier noted that most of Dr. Cook's findings referred to somatic pain, and asked if Dr. Cook had investigated visceral sensitivity in the same veteran population. Dr. Pellier referenced irritable bowel syndrome (IBS) studies that found a population with high visceral sensitivity, but also had a heightened threshold to somatic pain. Dr. Cook stated that this particular study hadn't looked at visceral pain, but agreed that it would be an interesting study to see if these sensitivities generalize to other types of stimuli. Dr. Pellier stated that he would expect Dr. Cook's study population to have a significant comorbidity with IBS, and suggested looking at comorbid outpatient risk conditions in future studies. Dr. Golomb stated that she believed there was a published study that examined visceral sensitivity in Gulf War veterans.

Dr. John Ottenweller gave the next presentation. He first spoke about his completed study entitled, "Plasma Cortisol, Paraoxonase and Butyrylcholinesterase in Gulf War Era Veterans." (See Appendix A - Presentation 4a.) Dr. Haley asked if the study model had used the Fukuda definition of multi-symptom illness. Dr. Ottenweller stated that it had. Dr. Golomb asked about the effects with chemical exposure, what happens with repeated low-level exposures, and whether there were subsets that didn't respond by normalizing their butylcholinesterase levels. Dr. Ottenweller stated that these questions hopefully would be dealt with in studies for which he had recently submitted grant proposals.

Next, Dr. Ottenweller gave a presentation entitled, "Paraoxonase Activity in Gulf War Era Veterans." (See Appendix A- Presentation 4b.) Following the presentation, Dr. Golomb and Dr. Meggs inquired about the study's methods. Dr. Ottenweller stated that the study was cross-sectional and that sample collection was tightly controlled.

Dr. Haley ask if Dr. Ottenweller would speculate why he was finding lower cortisol levels in deployed and more impaired veterans. Dr. Haley noted Dr. Rogene's Henderson's sarin animal model studies' findings of low cortisol levels, and her plans to conduct observational human studies as a follow-up. Dr. Ottenweller stated that another side of his research focused on stress models in rats. He stated that, clearly in the short term, there would be an elevation in adrenal function in chronic stress conditions with

persistent effects. However, he noted that most of the study veterans were being examined for chronic fatigue. He speculated that initial high stress levels might turn into lower cortisol levels once chronic illness occurs. Thus, hyperactivity of the adrenal may reduce the set point for the control of the adrenal axis, and drive levels of cortisol down to a low normal range. This, he stated, would produce significantly different findings from healthy veterans and controls. He noted that the question remained whether giving cortisol would help raise these low levels.

The meeting adjourned at 10:55 a.m. for a break.

The meeting reconvened at 11:07 a.m.

Dr. H. Liesel Copeland presented an overview of her ongoing research. First, she discussed the WRIISC's work in the development of a risk perception questionnaire. (See Appendix A – Presentation 5a.) Mr. Joel Graves expressed interest in reviewing this questionnaire, which Dr. Copeland offered to forward to him. Dr. Copeland also discussed her work in evaluating bioterrorism preparedness campaigns for veterans, as well as posttraumatic stress disorder (PTSD) clinical practice guidelines for veterans. (See Appendix A – Presentation 5b and 5c.)

Next, Dr. Natelson discussed an ongoing study, on which he is collaborating with Dr. Cook, regarding stress responses in Gulf War veterans. (See Appendix A – Presentation 6.) He explained that the study would look at two areas: (1) pituitary/adrenal function, and (2) negative feedback responses.

WRIISC Research II: Ongoing studies

Dr. Tom Findley, MD, PhD
Associate Research Director, East Orange, NJ, WRIISC

Dr. Findley discussed his ongoing study dealing with pilot data on balance in unexplained illness. (See Appendix A – Presentation 7.) He noted that this study used a system of six different testing conditions.

Dr. Meggs asked whether the abnormality appeared if only the first two conditions were considered. Dr. Findley stated that it did not. However, he was working with a team of mathematicians and engineers to develop more sophisticated processes/software to detect subtle changes in these two test conditions.

Dr. Findley noted that there is a high correlation between balance and health perception.

Dr. Haley stated that his experience using this equipment on Gulf War veterans hadn't revealed much information. He stated that his laboratory had detected some abnormalities, but he believed that the test was susceptible to unconscious exaggeration of the subjects' responses. He suggested that the WRIISC thoroughly explore this possibility, and be prepared to address this concern.

Dr. Findley discussed the history and development of structural integration treatments, and their use for treating chronic fatigue and fibromyalgia. Mr. Robinson indicated that he had heard positive reports from several ill veterans who had tried Rolfing as a treatment for their ailments. Dr. Findley stated that they were accumulating pilot data for a grant application to the National Academy of Complementary and Alternative Medicine (NACAM) for a study of Rolfing treatment as a therapy for Gulf War veterans. Chairman Binns noted that there should be VA funds in 2005 for pilot treatment trials such as this.

Chairman Binns introduced Dr. Sharon Mates, Dr. Allen Fienberg and Dr. Gretchen Snyder, who are colleagues of Dr. Greengard at Intracellular Therapies, Inc. He noted that Dr. Fienberg would be speaking on Tuesday about their planned research in this area.

The meeting adjourned at 11:50 a.m. for lunch.

The meeting reconvened at 12:55 p.m.

WRIISC Research III: New and planned research studies, including Deployment Health Research Enhancement Award Program

Dr. Karen Quigley, PhD
Dr. Dane Cook, PhD
Dr. Don Ciccone, PhD
Dr. Drew Helmer, MD
Dr. Kevin Beck, PhD
Dr. John Ottenweller, PhD

Dr. Natelson informed the Committee that the WRIISC had received two $50,000 pilot study grants for projects to be conducted by Dr. Karen Quigley and Dr. Cook.

Dr. Quigley discussed her newly NIH-funded MERIT study relating to risk perception and the psychobiological sequelae of vaccination. (See Appendix A – Presentation 8a.) She stated that one of their focuses was to develop a vaccine information sheet. She indicated that initial findings suggested that individuals were more trusting of information from Centers for Disease Control (CDC) than their local health authorities.

Dr. Quigley then discussed her second study, which was entitled: "Prospective Study of Functional Status in Veterans at Risk for Medically Unexplained Symptoms." (See Appendix A – Presentation 8b.)

Dr. Dane Cook discussed his newly funded study, which was entitled: "Functional Imaging of Pain in Veterans with Unexplained Muscle Pain." (See Appendix A – Presentation 9.)

The meeting's discussion shifted to proposed WRIISC research studies. Dr. Natelson stated that the WRIISC had submitted nine proposals under VA's recent Gulf War illness Request for Proposals (RFP) for funding consideration.

Dr. Don Ciccone presented his proposed study regarding online treatment for veterans with war-related multi-symptom illness. (See Appendix A – Presentation 10.)

Dr. Melling inquired if this avenue of study was based on an underlying assumption that Gulf War illness was stress-related vs. a physiological problem. Dr. Natelson stated that this wasn't a correct assumption. He stated that coping with illness was a very subjective thing, which was influenced by the veterans' attitudes and communications with their doctor. He stated that none of these treatments speak to the pathophysiology of the disease, but do speak to how to make someone sick do better.

Dr. Golomb expressed her concern regarding Dr. Ciccone's presentation of Gulf War veterans' complaints as being stress-related. Dr. Ciccone disagreed with Dr. Golomb's characterization. Discussion occurred about the influence of stress on Gulf War veterans' illnesses.

Dr. Haley commented that in the large exercise trial the outcome measure was the SF36 score. He stated that researchers needed to get beyond this measurement, because of the small-observed improvement and the likelihood that CBT was treating depression, and not the underlying disease. He noted that researchers needed to differentiate between relieving the stress and anxiety of a patient from conditions induced by stress, because the message that politicians and the public are hearing is that psychotherapy is a cure for Gulf War illness. To benefit veterans, Dr. Haley stated that scientists needed to be careful when they publish and talk about stress-reduction and –relief studies on Gulf War veterans. Dr. Ciccone indicated that he doesn't like to use the term stress-related illness, but medically unexplained illness.

Mr. Robinson asked Dr. Ciccone why he had referred to it as "stress" when it is "medically unexplained." Dr. Ciccone explained that stress is often a response to illness of an organic etiology. He noted that this stress can exacerbate the illness. He stated that their research was focused on helping the veterans cope with this stress. Mr. Robinson stated that veterans who had undergone cognitive behavior therapy (CBT) found that it was just a coping mechanism that didn't address the physical symptoms or illness.

Mr. Robinson noted that a recent study, the VA CBT study, found CBT provided a limited benefit, but this benefit waned as time passed and CBT was discontinued. He questioned the purpose of investigating on-line CBT unless one was going to interact daily with these veterans. Dr. Ciccone indicated that his study was related to, but not based on, stress. He noted that CBT is a term that is applied to a wide range of techniques and discussed the research done in this area. Dr. Natelson stated that it is important to step back and evaluate which parts of CBT are working - the C(ognitive) or the B(ehavioral). He indicated that this was unresolved and could be approached through small pilot studies.

Chairman Binns thanked Dr. Ciccone.

Dr. Helena Chandler, a NIH post-doctoral fellow at the WRIISC, presented her recently-funded study concerning Internet disclosure treatment for multisymptom illness. (See Appendix A – Presentation 11.) Mr. Robinson inquired about the funding for this study. Dr. Chandler stated that it was being funded by HRQ with the Department of Health and Human Services, which is affiliated with NIH. Mr. Robinson asked whether this study was affiliated with Project De-Stress at Walter Reed Army Medical Center. Dr. Chandler indicated that it wasn't, and that this was a pilot study to determine if this was a feasible approach. Dr. Natelson stated that this approach was remarkable, from a practitioner viewpoint, because it was simple Freudian therapy. He stated that this might be a potential treatment to help the veteran feel better.

Dr. Melling inquired whether this study would evaluate the difference in emotional release an individual gets from talking to himself/herself or writing on a piece of paper, versus receiving feedback from another individual. He wondered if previous online studies showed benefit because this was a new technology at the time, and hence was getting attention. Dr. Chandler indicated that she would like to follow up, including evaluation of a third group that would write about an ordinary life event. She did agree that further study does need to examine why this technique seems to work. Dr. Ciccone noted that writing alone had shown to provide a benefit.

Dr. Nicola Cherry asked whether there were concerns about doing harm to the veterans with this technique. Dr. Natelson acknowledged the need for care and caution, especially with suicidal thoughts. Dr. Chandler indicated that she would: (1) be reviewing the writings; (2) give the veteran contact information so she could reach them personally at any point; and (3) identified emergency assistance in the veteran's particular area.

Ms. Knox noted that Gulf War veterans really don't consume more services than any other veterans. She asked, in light of this, what prompted study into how to decrease the utilization of services by these veterans. Dr. Natelson agreed that Gulf War veterans didn't consume more services than other conflict veterans. He noted that some utilize no services, while some consume a lot. He stated that this study was targeting the highest consuming Gulf War veterans, and with a hope to reduce these veterans' angst.

Mr. Smithson inquired how "too much consumption" of healthcare services was determined. Dr. Chandler stated that a percentile threshold of the top 20%.

Mr. Robinson stated that most of the Gulf War veterans with an unexplained illness also have a diagnosed illness. He asked how this treatment would affect their access to services. Dr. Chandler indicated that it wouldn't prevent access, just gauge whether it would reduce their usage. Mr. Robinson asked if this study would include questions as to whether these veterans have pending claims. He noted that veterans with pending claims may, perhaps, be seeking treatment because they wish to have a diagnosis for benefit eligibility. Dr. Chandler indicated that this would be included in the questionnaire, and part of a secondary analysis of the study's data.

Chairman Binns thanked Dr. Chandler.

Dr. Natelson introduced Dr. Drew Helmer, who recently had received a three-year research career development award. He gave a presentation about the provider effects on outpatient utilization in veterans with symptoms. (See Appendix A – Presentation 12.)

Mr. Graves expressed interest in the Committee receiving annual progress reports on Dr. Helmer's research. Dr. Helmer indicated that he would be happy to provide one.

Dr. Steele inquired if the study would look at whether clinical practice changes occurred with knowledge of the clinical guidelines. Dr. Helmer stated that this was a tough question because there weren't quality measures/indicators. He indicated that he would be proposing a baseline assessment and, in a small pilot study, ask the veterans how their healthcare providers communicated with them.

Dr. Melling inquired about the degree of integration of this study with Dr. Chandler's and Dr. Ciccone's studies. Dr. Helmer stated they were aware of each other's work and were trying to pool resources and coordinate efforts. He stated that this coordination would centralize subject recruitment, and help avoid overstudy of a small group of veterans.

Mr. Robinson asked if VA physicians would be questioned about their own knowledge of Gulf War research. He stated that the lack of this knowledge was one of the biggest problems facing ill Gulf War veterans. Dr. Helmer stated that it was a very important question his research would address. Mr. Robinson stated that veterans were finding that they had to become subject matter experts and provide their physicians with the background information on their condition(s) and unique occupational exposures. He stated that VACO was not requiring physicians to have mandatory training in this area. Dr. Golomb stated that VA did have a mandatory training program several years ago that should be completely revised with the subsequent research in this area. Dr. Helmer stated that he hoped to examine four different VA sites, providing a wide basis for analysis, to address this matter.

Chairman Binns thanked Dr. Helmer.

Dr. Ottenweller introduced Dr. Kevin Beck. Dr. Beck gave a presentation regarding Dr. Servatius and his research proposal entitled, "Pavlovian Conditioning of Interoceptive Stress Reactions: A Model for the

Development of Unexplained Symptoms." Dr. Beck stated that they wished to take a different approach to determining how PB might cause later problems in individuals. They believed their proposed research might provide a model to explain how some unexplained symptoms occur in any deployment situation. Dr. Beck noted that their hypothesis was based on earlier work with morphine withdrawal and environmental cues.

Dr. Haley and Dr. Golomb questioned how this research would translate into an explanation of Gulf War veterans' symptoms. Dr. Beck stated this was only a possible mechanism that might explain some of the veterans' symptoms.

Dr. Natelson noted that the Committee were tough reviewers, and stated there were no animal models that really addressed behavioral questions. He stated that this approach was unique in examining how learned factors could lead to persistent symptoms. Chairman Binns asked what the recurring stimuli might be. He noted that most of the ill Gulf War veterans don't have sporadic symptoms. Dr. Natelson acknowledged there were problems with animal models, and that not any one soldier's symptoms would be explained. He stated that it would help in the understanding of how symptoms could be generated by the pairing of unappreciated neutral stimuli/environmental cues.

Dr. John Ottenweller thanked the Committee for its support of the recent Gulf War research-funding announcement (RFA). Dr. Ottenweller provided an overview of eight proposals, including two pilot projects, submitted by the WRIISC, covering various research areas including: PTSD, telemedicine treatment, musculoskeletal concerns, determinants of vulnerability to pyridostigmine bromide, immunology, and epidemiology. (See Appendix A – Presentation 13.)

Dr. Ottenweller also discussed the East Orange WRIISC's Research Enhancement Award Program (REAP) application, which was to be submitted that week. He reported that their research plans included stress reactivity testing and establishment of particular measures, followed by short pilot treatment studies, which would include cognitive behavioral therapy and exercise. Dr. Ottenweller discussed how these pilot treatment studies would be designed and monitored. Dr. Ottenweller discussed the WRIISC new post-doctoral fellowship program, and plans for developing clinical databases/computer-guided work-ups for Gulf War veterans.

Chairman Binns thanked the WRIISC researchers for their presentations and their research efforts on behalf of Gulf War veterans. He congratulated Dr. Natelson for attracting and inspiring a variety of researchers from different areas to work on these difficult illnesses, all with the goal of finding answers and making a difference in the health of veterans. He reassured the researchers that the Committee wasn't there to pass judgment on the proposed research, but noted that the Committee was preparing a report that hopefully would guide VA research decisions in the future. He stated that one of the general themes of the report was that stress as an underlying cause was not a hypothesis supported by more recent research. He noted that VA, in the past and relative to the number of diagnosed psychiatric disease cases, had more generously funded psychiatric research. He noted that 58% of VA's 2003 research funds went towards stress and anxiety-related studies. He stated, if the report was heeded, this percentage would decline.

Dr. Ottenweller stated that the group did have other research goals and directions for Gulf War research. With respect to clinical research, he discussed several areas, including: multidisciplinary research, identification of Gulf veteran subgroups with distinctive problems, comorbid physical and psychological conditions, brain imaging for neurological problems, animal studies on subclinical neurotoxicity, implementation research to educate VA clinicians, and risk perception/communication research. With respect to clinical trials, he discussed several goals, including: determination of how subgroups may respond differently, achieving better outcome measures, improving patient compliance, determination of

which components of cognitive behavioral therapy and exercise provide relief for veterans, and low-dose cortisol treatments.

The meeting was adjourned at 3:32 p.m. for a break.

The meeting reconvened at 3:48 p.m.

Review of WRIISC Education/Risk Communication/Clinical Missions

Dr. Gudrun Lange, PhD, Associate Director of Education, East Orange, NJ, WRIISC
Dr. Drew Helmer, MD, Associate Clinical Director, East Orange, NJ, WRIISC

Dr. Natelson stated that the next presentations would cover aspects of the WRIISC's three other program areas: Education, Risk Communication and Clinical. He noted that the WRIISC's clinical component focused on evaluating veterans from prior conflicts, but was shifting towards evaluating Operation Iraqi Freedom/Operation Enduring Freedom (OIF/OEF) returning veterans.

Dr. Natelson introduced Dr. Gudrun Lange, who was the WRIISC's Associate Director of Education. She discussed the WRIISC's patient education resource book and video library. She stated that the WRIISC also provides education to clinicians, including monthly local faculty/staff meetings on unexplained illness. She stated that they were developing a computer interface for VA/DOD guidelines for medically unexplained illnesses.

Dr. Lange also discussed the WRIISC's efforts in risk communication. She stated that the risk communication researchers interacted with the clinical arm of the WRIISC, in an effort to facilitate communication in an atmosphere of trust. She stated that they were working to develop patient-friendly summaries to help the veteran understand the results of their WRIISC clinical evaluation.

Dr. Natelson introduced Dr. Drew Helmer, the WRIISC's Associate Clinical Director, again. Dr. Helmer presented an overview of the WRIISC's clinical program. (See Appendix A – Presentation 14.)

Dr. Helmer addressed the referral process for seeking an evaluation at the WRIISC. He stated that a VA primary care provider must provide a referral. Dr. Golomb asked where a VA primary care provider would find the computerized referral forms. Dr. Helmer stated that they were mandated to be available in the VA's electronic medical records system, but noted that he didn't think many medical centers had downloaded the patch. Dr. Golomb stated that she had never seen this form in the computer system of the VA at which she practiced.

Dr. Steele asked whether VA clinicians were aware of the WRIISC centers. Dr. Helmer stated that this was a problem. He related a story about a veteran who made printouts of the WRIISC's website, but the clinician still contended that there was no such center. He stated that VA central office was working to educate the clinicians about the WRIISCs.

Dr. Helmer stated that only nineteen of the fifty-two veterans evaluated at the WRIISC were from outside the New Jersey VA health care system.

Mr. Robinson asked whether the VA was going to do a registry for the returning OIF/OEF veterans. Dr. Natelson stated he wished he was able to collect this data, but needed the funds to do it. Mr. Robinson suggested that VA funding for this initiative could be sought from Congress. Dr. Natelson said there

were also logistic problems, but that he would love to mobilize a group of individuals who could put this plan in action.

Dr. Steele asked when the clinic began seeing patients. Dr. Helmer said that they had started seeing veterans in 2002, with a brief interruption for a couple of months due to a bureaucratic glitch.

Mr. Smithson inquired if any of the referred, but not evaluated, veterans had been turned away due to travel funding problems. Dr. Helmer stated this hadn't been the case. He indicated the main reason the veterans hadn't been evaluated was due to the veteran's lack of response to the WRIISC's contacts/requests for information.

Dr. Helmer reviewed the demographics of veterans who had been seen at the East Orange WRIISC. He noted that 67% of the veterans evaluated were from the Gulf War. He reviewed the evaluation process, tests, inquiries and follow-up. He stated that the WRIISC didn't treat the veterans, but did make treatment recommendations to the veteran's local VA primary care provider.

Dr. Haley requested clarification of the WRIISC evaluation process. Dr. Helmer stated they used the standardized instruments recommended in the guidelines and generally explained the process. He said that the evaluation process takes approximately 2 ½ days, though they were working to streamline the process.

Dr. Natelson stated that the WRIISC looked forward to evaluating and caring for the troops involved in the current Iraq conflict. He stated that the WRIISC could examine 8 Iraqi veterans per week.

Clinical Evaluations of Gulf War and OEF/OIF Veterans

Dr. Ronald Teichman, MD, East Orange, NJ, WRIISC clinician

Dr. Natelson introduced Dr. Ronald Teichman, who provided an outline of the WRIISC's clinical evaluation procedures and questionnaires. He stated that evaluations had been streamlined, resulting in OEF/OIF evaluations taking 6.25 hours and prior conflict evaluation taking 9.0 hours. He stated that they were anticipating their first OEF veterans to arrive for evaluation on July 1, 2004. For prior conflict veterans, he indicated that the WRIISC could evaluate 3-4 referred veterans per day. He expressed his hope to evaluate OEF/OIF veterans with health-related concerns within months of returning stateside.

Chairman Binns noted that the WRIISC's findings had shown ways to objectively evaluate different types of illnesses, but questioned the elimination of several tests in the streamlining of the evaluation. Dr. Teichman stated that the balance test had been eliminated because it was abnormal in all of the veterans, which didn't allow for identification of subpopulations. Dr. Golomb asked if these abnormal results were observed in all veterans, regardless of conflict, and if these were observed or published data results. Dr. Teichman stated published data provided the basis for comparison with Gulf veterans. Dr. Natelson also noted that they didn't have controls (healthy Gulf War veterans) to compare. Dr. Golomb noted that the other veterans might be older and may be exhibiting problems due to age. Dr. Natelson acknowledged this possibility. Dr. Natelson stated the WRIISC's goal was to offer the veterans an "executive health evaluation."

Dr. Teichman noted that they were trying to get recently demobilized veterans, but it was difficult. Mr. Robinson mentioned that questionnaires were given to returning veterans while receiving care at Walter Reed Army Medical Hospital, and wondered if these were similar questions/answers to information that

WRIISC researchers would be interested in obtaining. Dr. Teichman noted that the definition of "healthy" was a potential stumbling block. He stated that most OEF/OIF veterans were seeking care from the VA for the same reasons as civilians of the same age group: musculoskeletal injuries, diabetes, psychiatric disorders, etc.

Dr. Golomb questioned whether the WRIISC was providing an evaluation different than that provided, or could be provided, by local VA primary care providers. Dr. Natelson stated that Desert Storm/Shield veterans weren't generally getting this type of evaluation at the local level. Dr. Golomb stated a more specialized evaluation, which included tests/procedures, e.g. cytokine measurements, that might not be conducted locally, might help encourage more referrals.

Dr. Teichman stated that another concern for the WRIISC was maintaining a line between clinical and research evaluations. Dr. Helmer agreed that this was a struggle. Discussion occurred about developing dynamic approaches, as well as individualized treatment plans for each veteran. Dr. Natelson stated the WRIISC also wanted to be a resource for local primary care physician(s) who aren't sure how to treat Gulf War veterans' complaints.

Overview and Discussion of Treatments for Unexplained Illnesses

Dr. Benjamin Natelson, MD
Executive Director, East Orange, NJ, WRIISC

Dr. Natelson invited a "brainstorming" discussion as to possible treatments for unexplained illnesses. He noted that the common symptoms of patients with unexplained illnesses included: fatigue, widespread pain, cognitive complaints and unrefreshing sleep. He reviewed the currently available drug treatments for these symptoms, and noted that these provided little, if any, effect.

Dr. Natelson also reviewed available rehabilitation approaches and techniques, which included: (1) gentle, physical conditioning; (2) cognitive behavioral therapy; and (3) Rolfing, which he indicated was an unproven and generally uncomfortable relief option. He stated these were the only available treatments, and that scientists/physicians needed to step back and evaluate where "we" should go next. He stated that the process required the patient's input and commitment to wellness.

Dr. Meggs noted that another key treatment category would be the identification of environmental triggers that may be playing a role in patient's unexplained illness. He stated that these environmental factors must be looked at in a systematic manner before a cognitive behavioral approach (that might suggest to the patient that there was no underlying cause) was taken. Dr. Natelson clarified that cognitive therapy didn't address disease etiology, but rather was directed at coping with disease symptoms in an effort to improve the patient's quality of life.

Chairman Binns asked Dr. Natelson if there were any other treatments that hadn't yet been proven objectively, e.g., Rolfing, but that he thought might be possibilities that should be further examined. Dr. Natelson noted it was difficult for the practitioner to know sometimes if a treatment worked for a patient. He stated that, if a patient didn't return to the physician's office, it may not be clear if the patient got better or whether he/she received no relief and gave up on that particular physician.

Dr. Natelson did note that recent fibromyalgia research showed one new treatment possibility. He referenced Dr. Karen Raphael's research, which examined first-degree family relations of fibromyalgia patients, and her findings that these individuals also have an increased rate of fibromyalgia and depression. Dr. Natelson stated this may indicate a relationship with serotonin levels, and thus suggest

use of anti-depressant medications for the treatment of widespread pain. Dr. Golomb noted that there were other neurotransmitters, such as acetylcholine, that were involved in pain.

Dr. Natelson asked the physicians in the audience for suggestions for possible treatment studies.

Mr. Robinson stated, while the Committee could not conduct clinical trials or investigations, it was very interested in knowing what treatments veterans were seeking on their own. He suggested that the WRIISC collect this information. He noted that the referred veterans seen at the WRIISC likely have been through every DoD/VA program. Dr. Natelson noted that a problem with collecting this information is "the wheelbarrow effect", which makes it hard to distinguish which individual treatment(s) might have helped that particular patient.

Chairman Binns asked the audience if they had any treatments to suggest for further research. Dr. Ciccone noted that the goal or "success" of a treatment was not always obvious. Dr. Natelson stated his definition of a "successful" treatment would be one that improved the quality of life and decreased symptoms. Mr. Robinson stated that a "successful" treatment, from most veterans' perspectives, is being able to understand what made them ill, but if that was not possible, to be able to move forward and return to as much a normal life as possible. Dr. Natelson concurred with this viewpoint. He stated that as a medical professor, he remained neutral as to the causes for Gulf War illness without more data, but remained committed to helping a patient improve his or her quality of life.

Chairman Binns asked if Dr. Natelson saw a difference between ill Gulf War veteran patients and ill civilian patients in terms of response to treatments. As the WRIISC's focus areas didn't include treatment, Dr. Natelson wasn't able to comment, but stated that he thought a pharmacological approach was viable. Discussion occurred about the multidiscipline approach and appropriate administration of pain management.

Chairman Binns asked if the WRIISC had put in a research proposal to study Gulf War veterans with respect to pain management. Dr. Natelson stated that the VA's Office of Research and Development (ORD) generally was interested in large, cooperative treatment trials. He stated that he explored pain management with the ORD officials, but they had expressed little interest in pursuing it.

Dr. Ciccone questioned how the Gulf War experience could be distinguished from civilian chronic unexplained pain. Chairman Binns stated he didn't see this as problem. He stated that the goal was to make a veteran feel better. If this resulted in help for a civilian with chronic fatigue syndrome, it would be insightful and an added benefit. Chairman Binns stated that the Committee's upcoming report would include a recommendation for more VA research with respect to treatments. He stated that the VA's central administration had indicated that it intended to expand research in this area.

Dr. Natelson suggested that small treatment trials be encouraged, but questioned whether VA had a mechanism or desire to do this. Roger Kaplan, Special Assistant to the VA Chief Research and Development Officer (CRADO), stated the focus may have been on large trials in the past, but that this was no longer the case. Dr. Natelson welcomed this news.

The meeting adjourned at 5:30 p.m. The Committee and audience members were invited to tour the WRIISC center facility.

The meeting reconvened the following day, June 29, 2004, at 8:30 a.m., in Room 11-137 of the East Orange, NJ, WRIISC.

Dr. Jack Melling and Ms. Marguerite Knox were not in attendance.

Update on VA ORD Gulf War Illnesses Research Initiatives and Activities

Mr. Roger Kaplan
Special Assistant to the VA Chief Research and Development Officer

Mr. Roger Kaplan provided the Committee with a status update on VA ORD Gulf War research initiatives and activities. (See Appendix A – Presentation 15.)

Dr. Steele inquired about the distribution of dedicated research funding between Gulf War illness and other deployment health concerns. Mr. Kaplan stated that 13 million dollars per year had been dedicated for Gulf War illness and deployment health concerns for the next four years. He indicated that it wasn't clear how these monies would be divided among the areas of research. Chairman Binns expressed concern, and stated that this wasn't his understanding of the funding situation for Gulf War illnesses. He indicated that he would investigate this matter further.

Dr. Golomb mentioned problems in obtaining VA grants to conduct studies with non-VA researchers. She asked for guidance as to how outside VA researchers could navigate the proposal process. Mr. Kaplan stated that the "five-eighths" rule was in place to ensure VA researchers were conducting the majority of VA-funded research. He noted that problems arose with outside research (with nominal VA principal investigators) because of the different review steps required by law, e.g. competitive bid, etc.

Dr. Golomb noted that the current regulatory requirements make it nearly impossible for outside researchers to conduct research in this area. Dr. Steele stated that she had heard reports of similar problems from other investigators. Mr. Kaplan stated that he would love to discuss this situation. He stated that some studies could be done with VA co-investigators as principal investigators (PIs) and limited VA appointments for research purposes.

Chairman Binns stated that ORD leadership did want to attract outside researchers, however, when applying current rules & regulations, this wasn't a process that VA was accustomed to following. He noted, though, that it wasn't uncommon to have some research work contracted outside VA. Mr. Kaplan acknowledged that there had been some sub-contracts on a limited basis/percentage of studies. He noted the total dollar amount was a key factor.

Dr. Pellier asked what prevented VA from allocating a certain percentage of research funds for outside research, which was subjected to the same rigorous scientific review and scrutiny. Mr. Kaplan stated that, unlike NIH, VA was not allowed to fund outside research. He stated that VA research was strictly intramural.

Dr. Golomb stated that Gulf War illness was a special problem effecting veterans. She noted that research funding for these conditions is not available outside of VA, e.g., NIH. Thus, due to VA ORD regulations and hurdles, she noted that non-VA researchers, who were desperately needed, would not be able to contribute to this field of study.

Chairman Binns acknowledged this was a serious issue, but there was no answer for it at the present.

Mr. Kaplan reported that plans were underway for the creation of a third WRIISC, with priority given to sites in the Western U.S. He noted that one of the research focus areas would be into health problems unique to women veterans, which would include sexual assault.

Chairman Binns stated that an additional WRIISC was an excellent idea. He noted, however, that the Committee would also like to see, as a separate entity, a Center of Excellence devoted to treatments. Mr. Kaplan stated that he hadn't had the opportunity to discuss this matter with the ORD leadership and didn't have solid guidance at this point.

Following Mr. Kaplan's presentation, Dr. Haley inquired about the status of the VA/NINDS joint Amyotrophic Lateral Sclerosis (ALS) program. He stated that he had heard that VA had pulled out of the project. Mr. Kaplan stated his understanding was that VA was committed to the program, but would investigate.

Mr. Kaplan reported that Dr. Stephan Fihn, MD, MPH, was the new acting CRADO. He will be spending part of his time in Washington, DC, and part in Seattle, WA, running the Center for Research Excellence which he heads. Dr. Aisen would be returning to her position as Director of Rehabilitation Research and Development.

Chairman Binns thanked Mr. Kaplan.

Acetylcholinesterase Activity in Gulf War Deployed and Era Veterans: June 2004 Update

John Concato, M.D., M.S., M.P.H.
West Haven Clinical Epidemiology Research Center (CERC)

Dr. John Concato provided the Committee with an interim summary report regarding his group's on-going study of AChE and other enzyme levels in ill Gulf War veterans. (See Appendix A – Presentation 16.)

Several Committee members inquired about the results related to levels of the read-through splice-variant, AChE-R. Dr. Concato stated he appreciated the importance of these results to the Committee. He noted, however, that it hadn't been emphasized in the original protocol received from VA ORD, and that based on the proposal's wording, wasn't slated to be performed because of results of the analyses in the original protocol. He did state that approval to perform AChE-R analysis had been given by Dr. Schuster, and preliminary results should be available at the Committee's October meeting.

Dr. Concato presented his research group's preliminary findings regarding AChE, BuChE, PON1, and arylesterase levels in ill Gulf War veterans. He noted that their most statistically significant finding, when comparing self-reported exposures and enzyme levels, was the correlation between PON levels and exposures to petrochemicals/solvents.

Dr. Haley stated that the Committee's interest or hypothesis was focused on the read-through, splice-variant AChE-R. He stated that he didn't think the listed exposures would affect the other enzymes. He stated that suspicion was focused on the exposures' effect on this mutant AChE. He wasn't sure how the concerns about the other enzymes were included in the original protocol. He stated that the Committee proposed a study idea, which went to a VA bureaucrat who changed it and returned it in a form that doesn't make sense. He stated that the researchers, including Dr. Concato, were one victim in this situation, and that the Committee was another victim. He noted, however, that the real victims were the veterans. He suggested the researchers and the Committee interface directly to avoid future problems.

Dr. Concato noted his concern about deviating from the original project proposal and the opportunity costs for going off into other directions that weren't delineated. Chairman Binns stated that the Committee appreciated the work that had been done, but noted that it really wasn't information that the Committee had requested. He suggested that, rather than fix it at further cost, it might be appropriate to let it "come back in" and make sure that the AChE-R levels were measured. Dr. Concato noted that the researchers do have interest in the other enzyme levels.

Discussion began as to what the Committee would suggest as a hypothesis re: AChE-R. Dr. Golomb suggested a hypothesis stating that elevated AChE-R levels would be observed in ill Gulf War veterans exposed to acetylcholinesterase (AChE) inhibitors. Dr. Haley suggested that the central question would relate simply to an association between Gulf War illness and AChE-R levels. Dr. Golomb stated it was very important to not dilute the real findings, and that at least one of the analyses had to involve a comparison of ill Gulf War veterans who self-report exposure to AChE inhibitors and healthy Gulf War veterans. Discussion occurred as to how the analysis might best be conducted.

Chairman Binns summarized the Committee's recommendation to focus on AChE-R enzyme levels in coming analyses. He noted that the Committee would not recommend continuing study into the other enzymes, nor performing a comparison between the Heritage study and ill Gulf War veterans. Dr. Concato expressed concern about the Committee's authority to alter the project proposal. Chairman Binns noted this concern, and stressed these were simply the Committee's recommendations. Mr. Kaplan indicated that the AChE-R studies should be pursued.

Dr. Concato asked the Committee to stratify or delineate the exposures it felt were the most pertinent. Dr. Golomb stated that there were three exposures on which to focus: intake of PB; belief or alerts that you were exposed to a chemical agent; and exposure to pesticides.

Dr. Haley noted that the Committee only wanted to look at this (AChE-R) research to see if it had promise. Chairman Binns agreed that the goal was to see if AChE-R levels were associated with Gulf War illness. If it were found to be a significant association, he stated that further study would be warranted.

Chairman Binns thanked Dr. Concato.

The meeting adjourned at 10:13 a.m. for a break

The meeting convened at 10:29 a.m.

Review of Recent Gulf War Research

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

Dr. Golomb gave a brief review of recent Gulf War research, including discussion about several reproductive health/birth defect epidemiologic studies. (See Appendix A – Presentation 17.) Dr. Haley expressed dismay that the authors of the *International Journal of Epidemiology* birth defect article failed to highlight significant findings in the article's abstract. Dr. Cherry commented that she believed the researchers probably felt the data were too weak to highlight with firm authority.

Mr. Robinson noted the variety of drugs being given to current Iraqi troops should be carefully followed.

Understanding the Neuronal and Biochemical Basis of Gulf War Illnesses

Dr. Sharon Mates, PhD, Chairman and CEO, Intracellular Therapies, Inc.
Dr. Allen Fienberg, PhD, Vice-President, Business Development, Intracellular Therapies, Inc.

Chairman Binns introduced Dr. Sharon Mates and Dr. Allen Fienberg.

Dr. Mates gave an overview of the formation of Intracellular Therapies, Inc. She stated that it was formed to commercialize the technology resulting from work done in Dr. Greengard's Rockefeller University laboratory. She stated that the company's research headquarters is located in New York City, near Columbia Presbyterian Hospital. She stated that the company has a network of consultants, including its Board of Directors, Special Advisory Board, and former Greengard lab team members.

Dr. Fienberg presented the scientific details behind Intracellular Therapies' plan to identify mechanisms related to effects of exposure to organophospates such as sarin, and potential treatments for Gulf War illness. (See Appendix A – Presentation 18.) He explained that their goal was to monitor changes in phosphorylation states in different cell types, looking at both direct and indirect pathways. Dr. Meggs inquired if these drugs were being screened to work inside or outside the cell. Dr. Fienberg stated that they were looking at surface receptors, but looking at the internal downstream cascade of each particular receptor. He also stated that they were looking at the integrated effects of phosphorylation at multiple receptor sites.

Mr. Robinson inquired whether brain biopsies were needed to identify phosphorylation markers that indicate exposure to sarin. Dr. Feinberg stated that there was evidence that some forms may be found in blood cells. Discussion occurred about the challenges of using animal vs. human models to discover these biochemical pathways.

Following Dr. Fienberg's presentation, Dr. Haley noted that the proposed research was geared towards analyzing immediate effects. He inquired about Dr. Fienberg's thoughts concerning long-term effects of sarin. Dr. Fienberg noted the differences between acute and chronic effects and the complex negative feedback loops associated with these pathways. Dr. Haley inquired if neuroplasticity and new dendritic cell growth would be examined in Dr. Fienberg's research. Dr. Fienberg noted that some of the proposed targets were involved in this process, and the targets had been chosen because of the wealth of information already available about them.

Dr. Pellier inquired if the research would be expanded to other pathways, including those used by secondary messengers. Dr. Fienberg indicated that there was an on-going effort in Dr. Greengard's laboratory to identify ways to study these different pathways

Chairman Binns inquired about non-cholinergic effects of anticholinesterases and whether these might be involved. Dr. Fienberg agreed that this was a possibility, and indicated that they intended to investigate if necessary.

Dr. Haley inquired whether they had identified key brain areas that were rich in the process being investigated. Dr. Fienberg noted the following areas: cortex, striatum, hippocampus, and amygdala. He noted that homologs were found in the brain stem as well.

Chairman Binns thanked Dr. Fienberg and Dr. Mates.

The meeting adjourned at 12:30 p.m. for lunch.

The meeting reconvened at 1:42 p.m.

Committee Business

Chairman Binns reported that he was investigating the apparent disconnects between VA ORD's morning presentation about future Gulf War Illnesses research and that which Secretary Principi had conveyed to him the previous week. Mr. Graves recognized the behind-the-scenes work being done by Chairman Binns and Dr. Steele to achieve more appropriate Gulf War illnesses research funding.

Chairman Binns noted that the Committee had left the last meeting unsatisfied with VA's FY2004 Gulf War illnesses initiative. He indicated that VA ORD had been very responsive to these concerns and expressed his belief that things would get on track. However, he acknowledged that it was one thing to agree in principle, but another to agree in practice implementation. He noted the Committee's desire to see a separate merit review panel for Gulf War illnesses, which was agreed to by VA ORD. However, when the panel emerged, he stated that it also included deployment health issues. He noted that the "devil was in the details."

Dr. Haley stated that the Committee needed to keep its focus on getting done what Secretary Principi and Deputy Secretary McKay had originally indicated would be VA's commitment towards Gulf War illnesses research. Chairman Binns acknowledged that the original plan was ambiguous in parts, such as in relation to funding for deployment health research in general, but that work with VA ORD was leading towards a 15 million dollar commitment for specific Gulf War illnesses research. He reported that the Secretary had stressed to him that he was very much in support of this plan, and wished to reinforce his commitment in this area.

Chairman Binns, Dr. Haley, and Dr. Golomb gave a brief report on an NINDS-sponsored conference they had attended in May on needed research related to effects of nerve agents. Dr. Golomb stated the conference was very eye-opening, and found the talks to be excellent. She was excited that high-quality scientists had given these presentations, who weren't predisposed to the viewpoint that there wasn't an issue or that there could not be a connection between low-level nerve agent exposures and health outcomes. She noted that there was interest, though no action, in issuing a request for proposals through NINDS on chemical warfare protection and neurobiology. She stated this might open up some funding for Gulf War illnesses research by outside, non-VA scientists.

Dr. Haley noted that DoD had co-sponsored this conference, and that talks were given on each class of chemicals that might be seen in a chemical terrorist attack. He stated that, for the first time in his experience, it was a given among the participants that low-level sarin exposure could have long-term effects. He noted that DoD's budget for studying long-term effects of low-level chemicals had been decimated with a shift towards deployment health concerns. He stated that NINDS interest in this area was developing because of the growing funds available for bioterrorism research.

Chairman Binns noted that the meeting had been well attended, with about 100 participants, representing DoD, NIH and other government agencies. He indicated that he found the meeting to be very productive and exciting because more researchers were becoming interested in this area. He stated there was a section where research agenda suggestions were solicited, and then reviewed by a steering committee. He noted that these ideas were now being reviewed within NIH.

Chairman Binns reported that several Committee members had testified before the House Committee on Government Reform earlier in the month. He stated that Mr. Robinson, Dr. Haley and himself had given

testimony. He indicated that the House Committee was very receptive to research into low-level chemical exposures. He stated there was some discussion for additional Gulf War illnesses research by other agencies, e.g., DoD and NIH.

Dr. Steele gave a brief overview of the progress on the draft Committee report. She indicated that she hoped to distribute the latest draft in the coming week. She stated that the intent was to cover the major ideas outlined in the Committee's interim report as well as summary recommendations generated the prior year, constructing a narrative, along with scientific references, to support these findings and recommendations. She stated that the report would cover topics addressed by the Committee in 2002 and 2003, with the exception of administration issues that had arisen in 2004. She noted that future reports would address other topics, including, but not limited to, depleted uranium and infectious diseases. She stated that this report had originally been drafted in the form of a somewhat brief memorandum to the Secretary, but it became clear that this report could serve a broader function by providing a more comprehensive summary and current evaluation of Gulf War illnesses research. She stated that the report was intended to reflect the consensus viewpoint of the Committee, balancing individual Committee member's views with individual differences voiced by Committee members.

Dr. Steele noted that there had not been many substantive or conceptual changes suggested in members' feedback on the prior draft of the report. She stated that most of the comments were focused on refining the report's terminology. She requested the Committee's input on the wording of certain things, along with the development of the report's "take home message."

Mr. Robinson stated that he would like to see a greater emphasis in the report's opening statement about the change in current motivation and scientific efforts into Gulf War illnesses research. He indicated that he was excited about the new direction of this research, and believed that the introduction needed to reflect this hope and emerging science. Mr. Smithson noted this hope and science was evident in the report's body, and agreed that the introduction needed to reflect this more.

The Committee discussed the report's title. The Committee's consensus was to have a more positive title. The Committee and audience discussed the differing viewpoints of the use of various terms and abbreviations, such as "medically unexplained illnesses", "chronic multisymptom illnesses", "undiagnosed illnesses", "Gulf War neurological syndrome", and "Gulf War illnesses".

Dr. Steele stated that there had been few changes in the specific recommendations set forth in the report from those discussed previously in Committee meetings. She noted, though, that Committee recommendations had focused on research concerns in accordance with its mission, and hadn't addressed clinical concerns, e.g., educational courses for VA physicians, clinical practice guidelines, etc. She stated that the Committee might wish to discuss what role it might have in addressing clinical issues such as those related to the care of Gulf War veterans.

Mr. Robinson stated that his reading of the Committee's charter didn't prohibit the Committee from making clinical recommendations. Chairman Binns stated that he believed many of these issues would come under the category of "disseminating research", and would be appropriate for the Committee to address. However, he noted that some purely clinical issues, e.g. patient load, may not be appropriate for the Committee to address. Discussion occurred about the goals of the Committee's report and the dissemination of its contents to VA researchers.

Mr. Smithson noted that the VA had not established an official ALS/Gulf War presumption for veterans seeking service benefits. He stated that the American Legion had contacted the Veterans Benefit Administration about this issue, and that they indicated it was premature to establish a presumption due to

several criticisms of the ALS research. He stated that the Committee may want to review and address these criticisms.

Dr. Pellier noted, for the record, that, despite the specific wording concerns discussed, the report was "a bloody good" one. The other Committee members agreed.

The meeting adjourned 2:52 p.m.