Research Advisory Committee on Gulf War Veterans' Illnesses

June 29-30, 2009, Committee Meeting Minutes

Boston University School of Public Health
Boston, MA

DEPARTMENT of VETERANS AFFAIRS

Research Advisory Committee on Gulf War Veterans' Illnesses
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I hereby certify the following minutes as being an accurate record of what transpired at the June 29-30, 2009 meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses.

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

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Attendance Record

Members of the Committee
James Binns, Chairman
Roberta White, Scientific Director
Floyd Bloom
Dedra Buchwald
Beatrice Golomb
Anthony Hardie
Marguerite Knox
Bill Meggs
Mary Nettleman
James O'Callaghan
Steve Smithson
Lea Steele

Committee Staff
Kimberly Sullivan
Sadie Richards
John Douglas

Designated Federal Officer
William Goldberg

Guest Speakers
Ronald Bach
Gordon Broderick
Philip De Fina
Douglas Dockery
Keith Kelley
Nancy Klimas
Marney Naeser
Meryl Nass

Abbreviations

AChE – Acetylcholinesterase

ALA – Alpha-Lipoic Acid

ALS – Amyotrophic Lateral Sclerosis

CFS – Chronic Fatigue Syndrome

CNS – Central Nervous System

CoQ10 – Co-enzyme Q10

CPAP – Continuous Positive Airway Pressure

CRISP – Computer Retrieval of Information on Scientific Projects

CSP – Cooperative Studies Program

DU – Depleted Uranium

EHS – Environmental Hazards Services

ERP – Event-Related Potentials

GERD – Gastroesophageal Reflux Disease

GWI – Gulf War Illness

HBOT – Hyperbaric Oxygen Therapy

IL-1 – Interleukin-1

LDN – Low Dose Naltrexone

LED – Light Emitting Diode

LLLT – Low-Level Laser Therapy

MEG – Magneto-Encephalography

MRI – Magnetic Resonance Imaging

MSS – Multi-Symptom Syndrome

NADH – Nicotinamide adenine dinucleotide

NIH – National Institutes of Health

NIRS – Near Infra-Red Spectroscopy

OP – Organophosphate

PB – Pyridostigmine Bromide

qEEG – Quantitative Electroencephalography

QOL – Quality of Life

RFA – Request for Application

sLORETA – Standardized Low Resolution Brain Electromagnetic Tomography

TBI – Traumatic Brain Injury

TMS – Transcranial Magnetic Stimulation

Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses
June 29-30, 2009
Boston University School of Public Health, Crosstown Center
801 Massachusetts Ave., Room 462, Boston, MA

Agenda
Monday, June 29, 2009

8:00 – 8:30	**Informal gathering, coffee**	
8:30 – 8:35	**Welcome, introductory remarks**	**Mr. Jim Binns, Chairman** **Res Adv Cmte Gulf War Illnesses**
8:35 – 9:30	**Kuwaiti oil well fire study**	**Dr. Douglas Dockery** **Harvard University School of Public Health**
9:30– 10:30	**Gulf War associated chronic coagulopathies update**	**Dr. Ronald Bach** **Minneapolis VA Medical Center**
10:30 – 10:45	**Break**	
10:45 – 11:15	**Impaired immune function in Gulf War illness**	**Dr. Nancy Klimas** **Miami VA Medical Center**
11:15 – 12:30	**Immune network remodeling in chronic fatigue syndrome**	**Dr. Gordon Broderick** **University of Alberta**
12:30 – 1:30	**Lunch**	
1:30 – 2:30	**The role of neuroinflammation in chronic illness**	**Dr. Keith Kelley** **University of Illinois at Urbana-Champaign**
2:30 – 3:15	**Symptom patterns and treatment strategies For fibromyalgia, GW illness and Military post-vaccination patients**	**Dr. Meryl Nass** **Mt. Desert Island Hospital**
3:15 – 3:30	**Break**	
3:30 – 4:15	**Update of VA Gulf War research**	**Dr. William Goldberg** **VA Office of Research and Development**
4:15 - 4:45	**Public Comment**	
4:45 – 5:30	**Discussion of potential GWI treatments**	**Res Adv Cmte Gulf War Illnesses** **And invited speakers**

Meeting of the Research Advisory Committee for Gulf War Veterans' Illnesses
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Boston University School of Public Health, Crosstown Center
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Agenda
Tuesday, June 30, 2009

8:00 – 8:30	**Informal gathering, coffee**	
8:30 – 9:30	**Potential treatment for cognitive dysfunction using transcranial laser/light emitting diodes**	**Dr. Marney Naeser** **VA Boston Healthcare System**
9:30 – 10:30	**Current therapies for fibromyalgia**	**Dr. Dedra Buchwald** **Res Adv Cmte Gulf War Illnesses**
10:30– 10:45	**Break**	
10:45 – 11:30	**Innovative therapies for mild brain injuries**	**Dr. Philip De Fina** **International Brain Research Foundation** **Kessler Institute for Rehabilitation**
11:30 – 12:30	**Public Comment**	
12:30 – 1:00	**Committee discussion**	**Res. Adv. Cmte Gulf War Illnesses**
1:00	**Adjourn**	

DAY 1

The June 29-30, 2009 meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses (hereinafter referred to as the Committee) was held in Room 462 & 462A of the Crosstown Center Building at the Boston University School of Public Health, 801 Massachusetts Avenue, Boston, MA.

Welcome & introductory remarks

Mr. James Binns, Committee Chairman
Dr. Roberta White, Committee Scientific Director

Chairman Binns called the meeting to order at 8:30am. Dr. White then introduced the newest Committee staff member, John Douglas. Before beginning the meeting, Dr. White recognized the volunteer advocacy efforts of Mr. Binns. Dr. White then announced the meeting's focus on mechanisms and potential treatments for Gulf War Illness (GWI), and introduced the first speaker, Dr. Douglas Dockery.

Kuwaiti longitudinal health study

Dr. Douglas Dockery, Harvard School of Public Health

Dr. Dockery, an expert on air pollution and health, spoke about his epidemiologic studies investigating the long term health effects of the Gulf War on the Kuwaiti population (See Appendix – Presentation 1). This ongoing public health survey compares members of the Kuwaiti population that were in country during the invasion and occupation with those Kuwaiti nationals who were outside of the country during this period. Exposure to violence and oil well fire smoke were associated with increased morbidity, and self-report data on Gulf War Syndrome symptoms await full analysis.

Dr. Golomb, a member of the Committee, asked whether Dr. Dockery had run any analyses to control for residual confounding variables associated with characteristics of vacationing vs. non-vacationing Kuwaiti nationals (e.g. severity of pre-existing chronic health conditions). Dr. Dockery replied that socioeconomic differences among his study population were not substantial.

Dr. Buchwald, a member of the Committee, asked Dr. Dockery about his data collection methods, and whether all family members were interviewed. Dr. Dockery replied that all data was self-reported, and that each participant reported only his/her own health status.

Dr. Steele, a member of the Committee, asked if Dr. Dockery has begun looking at associations between some of the health and mortality outcomes in relation to the oil well fire exposure levels. Dr. Dockery replied that detailed analyses conducted for each individual revealed fairly modest association. He added that the smoke from the southern oil well fires mostly blew away from the local populations.

Mr. Hardie, a member of the Committee, then asked Dr. Dockery if he felt the pattern of symptoms reported by his Kuwaiti participants mirrored those found in ill Gulf War veterans. Dr. Dockery replied that the results needed to undergo further analysis to answer that question.

Dr. Nettleman, a member of the Committee, asked if cultural or bureaucratic factors contributed to the difficulty in determining cause of death in Dr. Dockery's study. Dr. Dockery replied that the barriers appeared to be more bureaucratic than cultural.

Dr. Meggs, a member of the Committee, asked Dr. Dockery to clarify his findings that circulatory events were more significantly associated with oil well fire smoke exposure than respiratory events. Dr. Dockery replied that these hazard ratios reflect the greater number of recorded deaths due to cardiovascular events, in comparison to the less frequently cited fatal respiratory events.

Dr. Bloom, a member of the Committee, asked if Dr. Dockery was aware of any other public health studies of populations exposed to brief wars. Dr. Dockery remarked that, while studies of populations in Kosovo have been conducted, these populations continue to face barriers to accessing health care, food and housing. Dr. Dockery found the Kuwaiti population unique in that their infrastructure and lifestyle were restored within a few years following the war, so that ongoing trauma and stress do not confound results.

Drawing on anecdotal evidence from his evaluations of three ill U.S. merchant marines exposed to oil well fire smoke during the Gulf War, Dr. Philip De Fina, a neuropsychologist and invited speaker, commented on the value of formal, objective testing to confirm the presence of neuropsychiatric symptoms. Dr. Dockery replied that he agreed, and had conducted some biological monitoring of the study subjects in addition to the self-report data he presented.

Dr. Meryl Nass, MD and invited speaker, commented on reports that she had heard of oil well fire smoke exposures in Saudi Arabia. She then asked whether traveling outside of Kuwait could necessarily serve as a reliable proxy for avoiding oil well fire smoke. Dr. Dockery replied that he had accessed records of where the Kuwaiti population vacated to, and acknowledged that some of the people who traveled south to Saudi Arabia could have been exposed to greater levels of oil well fire smoke.

Dr. Nass then asked what particulates the Kuwaiti population was exposed to. Dr. Dockery replied that these particulates were classified as PM2.5 with toxicity comparable to particulate matters found in samples from the urban U.S., though in much higher concentrations (many micrograms per cubic meter).

Mr. Hardie, a member of the Committee, attested to the highly concentrated clouds of particulate matter that he and other Gulf War veterans were exposed to. After describing the thick smog to which he was exposed, Mr. Hardie commented that he and his compatriots coughed up black sputum for the last 2 months during his deployment and for the first month after his return from the Gulf War. Mr. Hardie concluded by

mentioning that his symptoms mirror those reported by the Kuwaiti nationals in Dr. Dockery's study.

Chairman Binns thanked Dr. Dockery for his presentation before Dr. White introduced the next speaker.

Tissue Factor and Gulf War-associated chronic coagulopathies update

Dr. Ronald Bach, Minneapolis VA Medical Center

Dr. Bach presented a summary of the results and conclusions from his blood coagulation study investigating the pathophysiology of GWI (See Appendix – Presentation 2). Dr. Bach reported indirect and direct evidence of coagulation system activation in ill Gulf War veterans, but stated that no inferences regarding causality can be drawn at this time. Interestingly, over 90 percent of the Gulf War veterans (with and without GWI symptoms) in this study had above average levels of thrombin-antithrombin complex and d-dimer than the ELISA kit reference populations. In a proteomic screen of 89 additional plasma protein antigen abnormalities, Dr. Bach found that coagulation factor VII antigen levels were elevated in most veterans symptomatic and asymptomatic for GWI in this study. Dr. Bach stated that in his future research, he would like to include a study group of veterans who were not ill with GWI or other diseases.

Reflecting on Dr. Bach's findings and implications for potential therapies, Dr. Meggs recalled a recent conversation he had with an environmental medicine specialist who uses environmental control units to isolate patients with diagnosable medical conditions from various environmental triggers (chemicals, etc.). This specialist remarked that patients with chronic recurrent deep vein thromboses benefit greatly from reduced exposure to environmental triggers. Dr. Bach commented that the coagulation system is intimately involved with the immune system.

Dr. O'Callaghan, a member of the Committee, asked Dr. Bach why he conducted the inflammatory proteomic screen as part of his study. Dr. Bach replied that he had not expected any results, but that including measures in addition to coagulation analyses broadened the study's scope. Dr. O'Callaghan then mentioned recent findings that prothrombin leads to activation of glia and subsequent neuroinflammation.

Dr. O'Callaghan then confirmed with Dr. Bach that he had independently run ELISA control samples to ensure that the assay was working properly.

Dr. Buchwald first expressed concern with the binary definition of GWI used in Dr. Bach's study. She also wanted to know the clinical significance of the differences in mean values (i.e. of thrombin-antithrombin and d-dimer) identified in the study. Lastly, Dr. Buchwald also asked Dr. Bach to identify the clinical correlation of the hypercoagulable state found in most study participants. Dr. Bach replied that his study's designation of GW veterans into binary groups was somewhat arbitrary. He added that hypercoagulation could manifest clinically as deep vein thrombosis, heart attacks, strokes

or other acute thrombotic events, but that he believed his study participants exhibited a different compensated chronic disseminated intravascular coagulation. Dr. Golomb then commented that she believed there to be a strong biological plausibility for a relationship of mild hypercoagulability to symptoms of the kind seen in Gulf War veterans. Dr. Bach agreed.

LTC Marguerite Knox, a member of the Committee, then asked why, if the clotting cascade is directly related to the immune system, only one antigen (tissue factor VII) of the 89 measured was found to be elevated. Dr. Bach replied that while he had expected to see elevated inflammatory markers as well, such abnormalities might only have been part of the initial process, and that the body may have adjusted so that altered biomarker levels were not part of the current (compensatory) steady state.

Dr. Nettleman expressed appreciation for Dr. Bach's pilot study, adding that a next good step to identifying potential biomarkers of GWI would be a hypothesis-driven study in a larger population. Dr. Bach remarked that the path of his study led in a different direction than originally expected, and that this warrants further investigation.

Dr. Steele encouraged Dr. Bach to refine his definition criteria for GWI in the follow-up study for which he has received funding. Dr. Bach agreed that this was necessary. Dr. Steele then asked what correlations are known about peripheral coagulability, coagulopathies and glial activation, cytokine production in the brain and cerebral blood perfusion. Dr. Bach replied that he had no specific comments, but that he sees hypercoagulopathy as a condition that can exist in the background without manifesting any symptoms but that individuals may be affected in unique ways. Anything that impairs circulation on the microcirculatory level could have ischemic effects that could, over time, result in irreversible changes in physiology that aren't immediately obviously connected to the coagulopathy. Dr. Bach added that large blood vessels might also be impacted in some individuals.

Dr. Nass stated that she has also used commercial d-dimer assays and found excess thrombosis in a small set of patients. She expressed her concern that these assays have a high false positive rate and a too-high false negative rate. She also said she would not rely on the factory standards provided by the d-dimer assay companies. Dr. Bach agreed, commenting that the kits were designed for studies of patients with more severe thromboses than those he is testing.

Chairman Binns then asked Dr. Bach to talk about the link between tissue factor and inflammation. Dr. Bach explained that, evolutionarily, tissue factor (originally a cytokine receptor) is the link between coagulation and inflammation and the immune system. Thus, things that affect the immune system are directly communicated to the coagulation system by way of tissue factor.

Dr. Golomb recalled reading somewhere that apoptosis is a trigger for coagulation. She asked Dr. Bach if tissue factor is the mechanism behind this. Dr. Bach replied that it is, explaining how tissue factor is found on the surface of the monocytes in an encrypted

(inactive) state. If a monocyte becomes apoptotic, the tissue factor is converted to its decrypted (active) state. The same process occurs on platelets as well, independent of gene expression, and this is part of a positive feedback loop whereby more thrombin is created which accelerates transfer of tissue factor from monocytes to platelets and so on.

LTC Knox asked whether the tissue factor being measured in Dr. Bach's study was encrypted, and he explained that his assays measure all tissue factor present, decrypting any that is encrypted during the assay.

At 10:32am Chairman Binns thanked Dr. Bach for his presentation, adding that more time would be available later in the afternoon for further discussion. The Committee took a brief break and reconvened at 10:45.

Dr. White then introduced Dr. Nancy Klimas.

Immune function in Gulf War Illness

Dr. Nancy Klimas, Miami VA Medical Center

Dr. Klimas provided an overview of immune impairment in GWI and chronic fatigue syndrome (CFS) prior to describing the genomic mapping study she and Dr. Broderick conducted in GWI and CFS patients subjected to exercise challenge (See Appendix – Presentation 3). At the conclusion of her presentation, Dr. Klimas showed preliminary data on differential gene expression in patients with GWI compared to CFS. She believes these results will provide valuable information regarding causality, homeostasis, and relapse triggers in GWI and CFS. Dr. Klimas then introduced Dr. Broderick.

Immune network remodeling in Chronic Fatigue Syndrome and Gulf War Illness

Dr. Gordon Broderick, University of Alberta

Prior to discussing his analysis of the preliminary study results presented by Dr. Klimas, Dr. Broderick presented his technique of mapping the association between specific gene sets and various molecular neuroendocrine signals in CFS and GWI patients (See Appendix – Presentation 4). Dr. Broderick stated that he hopes to use his multi-level data to build a classification model capable of discriminating patients with GWI from other ill patients (e.g. with CFS) and healthy individuals.

Dr. Meggs asked how the values in Features 1 and 2 (see slides 13-16) were calculated. Dr. Broderick explained that these were weighted averages. Dr. Nettleman asked if these weighted averages were determined from the same population that they are being applied to in his current study. Dr. Broderick replied that the sample population of Gulf War veterans served as the source of the weighted average, but that the stability of the average was tested.

Dr. Bloom commented that the data are very convincing to differentiate subjects with GWI diagnoses from healthy controls, and asked whether Drs. Broderick and Klimas believe that the differences are descriptive of the disease or the consequences of having the disease. Dr. Klimas replied that although this is unknown, approaches to interventive change can be developed without this knowledge. Dr. Bloom then asked whether the existing data suggest a way to intervene in a positive sense. Dr. Klimas said she believed so, and Dr. Broderick replied that the networks provide a powerful tool for examining potential interventions, particularly if future analyses involve more frequent sampling over a greater period of time (as opposed to measurements taken at only three points in time). Dr. Bloom then asked if any of the study participants were healthy enough to be tested again. Dr. Klimas replied that many were willing and able to participate in future studies. Drs. Klimas and Broderick then briefly discussed the therapeutic utility of complex mathematical modeling of receptor kinetics, biochemistry and homeostasis in patients with GWI and similar chronic diseases.

Dr. Keith Kelley, a neuroimmunologist and invited speaker, asked how – from a pharmaceutical approach – an intervention should be designed, given the complexity of the networks involved in GWI. Dr. Broderick replied that, ideally, everything would be measured at extremely high frequency, but he acknowledged the existence of a significant hidden state in human systems. Dr. Broderick believes that his numerical models are useful for screening therapeutic candidates, but that animal models and other approaches will be necessary to reveal any unanticipated side effects.

Dr. Steele asked if Dr. Broderick had compared the baseline, steady-state network model of CFS patients (data from a previous study) to the steady-state network of patients with GWI. Dr. Broderick replied that he had not, because the datasets differed greatly because detailed immune profiling at the cellular, intercellular, and DNA expression levels was available for GWI patients but not the CFS patients.

Dr. Steele then asked about feature 1 (as displayed in slide 14), and whether it alone could be used to differentiate ill from well Gulf War veterans. Dr. Broderick replied that unfortunately this would not completely distinguish ill from well Gulf War veterans. Dr. Klimas added that the proteomic assays used in feature 1 and feature 2 were not terribly expensive.

Dr. Steele asked if similar studies had been done on diseases other than CFS and GWI. Dr. Broderick replied that he would like to look at lupus, arthritis and other inflammatory diseases. Dr. Klimas mentioned that public access genomic datasets could be used in comparative analyses of different diseases.

Dr. Steele asked Dr. Klimas what definition of GWI she had used. Dr. Klimas said that she used Fukuda's 1998 chronic multisymptom illness criteria and CFS exclusions for the Gulf War cohort. She added that the study had involved detailed medical chart reviews in order to exclude subjects suffering from other confounding health disorders.

At 12:25pm Chairman Binns thanked Drs. Klimas and Broderick and called for an hour lunch break.

The meeting reconvened at 1:45, when Dr. White introduced Dr. Keith Kelley.

The role of neuroinflammation in chronic illness

Dr. Keith Kelley, University of Illinois at Urbana-Champaign

Dr. Kelley discussed the minimal requirements for neuroinflammation, and provided an overview of relevant experiments he has conducted in pre-clinical animal models investigating mechanisms involved in pain, exercise and fatigue, difficulties in learning memory, and mood changes (symptoms common to veterans with GWI) (see Appendix – Presentation 5). In his research, Dr. Kelley has found that neuroinflammation reduces appetite and motivation, increases exhaustive fatigue, increases sensitivity to pain, causes deficits in learning and memory, and induces depressive-like behaviors. Given the lack of treatments for GWI, Dr. Kelley believes the neuroinflammation hypothesis is worth testing because FDA-approved drugs to reduce neuroinflammation and pre-clinical animal research models are readily available.

Dr. O'Callaghan asked if Dr. Kelley had looked at primed and activated conditions, morphologically. Dr. Kelley replied that he had, and that he doesn't believe morphological differences can be detected between an activated and resting microglial cell, using the markers that he has. Dr. O'Callaghan followed up by mentioning Dr. Wolfgang J. Strite's research on senescent microglial cells. Dr. Kelley replied that much remains unknown about glial cells.

Dr. Steele asked if any models of peripheral and central cytokine activation suggest evidence for persistent CNS inflammation (e.g. 18 years after initial exposure). Dr. Kelley replied that he believed Hugh Perry had conducted some research with prion diseases in which peripheral cytokine levels rose and fell, with central cytokine levels remaining elevated over time.

Dr. Golomb commented that primary peripheral processes can have very important central nervous system consequences, and that seeing the brain affected doesn't inherently mean that the primary process is purely central. Dr. Kelley replied that systemic inflammation can induce depressive-like behaviors, and that he does not know if the activation of this response occurs in the periphery or the brain. Dr. Kelley called for greater research into the communication systems between the brain and the body. Dr. Kelley believes that the best models to address the issue in question are those in which inflammatory stimulation is applied perinatally.

Dr. Steele then asked if the location of microglial activation affects the types of behaviors seen in mice. Dr. Kelley replied that he is not a neuroscientist, but that his research has not revealed much evidence of that. He views the system as diffuse. Dr. Steele added that Linda Watkins' work on persistent pain suggests that glial activation in the spinal cord

may exert effects on the brain. Dr. Steele then expressed concern that not many researchers are studying the glia with respect to toxic exposures. She then asked Dr. Kelley if he believed acetylcholine has some regulatory effect on inflammation in the brain. Dr. Kelley replied that although acetylcholine appears to have an anti-inflammatory effect in the periphery, further studies must be conducted to elucidate its effect in the brain. He believes mouse models may prove useful in this research.

Dr. Golomb then asked Dr. Kelley about his studies with Interleukin-1 (IL-1) agonists and antagonists, and whether the findings mean that peripheral effects alone are adequate to produce some of the behavioral effects seen. Dr. Kelley replied that this could be the case, and that it is probably a dose-response issue.

Dr. Klimas asked Dr. Kelley how he would measure microglial activation in humans, and whether any systemic measure could serve as a surrogate. Dr. Kelley replied that the peripheral benzodiazepine receptor has been used in challenging and debilitating autoimmune diseases, but that further work is necessary.

Dr. Steele asked Dr. Kelley to explain the rationale behind soluble fiber being used to help alleviate neuroinflammation. Dr. Kelley replied that a colleague has found that pectin, a soluble fiber found in mouse chow, promotes the synthesis of IL1 receptor antagonist in the brain of mice. Dr. Steele commented that she knew of a clinician in Maryland who uses cholestyramine (a soluble fiber) to treat cases of neurotoxicant poisoning. Dr. Golomb added that it is also being used to treat mold toxins.

Chairman Binns then thanked Dr. Kelley, and Dr. White introduced Dr. Meryl Nass.

Symptom patterns and Treatment Methods for Gulf War illness and multi-symptom syndrome patients

Dr. Meryl Nass, Mount Desert Island Hospital

Dr. Nass, who has treated hundreds of patients with chronic multi-symptom syndromes (MSS), provided an overview of her treatment program and discussed the cases of 20 patients (5 of whom were Gulf War veterans) that she has seen (see Appendix – Presentation 6). Dr. Nass explained that her patient-centered approach involves thorough evaluations and comprehensive treatment regimens. She reported incorporating elements to address pain, sleep, nutrition, gastrointestinal complaints, and chemical sensitivity.

Dr. Golomb commented on the frequency with which obstructive sleep apnea is identified in her patients. About half of the patients Dr. Nass has sent to be tested are diagnosed with sleep apnea. Dr. Klimas stated that in her chronic fatigue patients, 60% of the women and 40% of the men sent to sleep studies had developed airway resistance sufficient to need continuous positive airway pressure (CPAP) over the course of their illness. Dr. Buchwald commented that in her studies she has found a greater proportion of sleep disorders than would be expected in the general population, particularly among

women. Dr. Buchwald added that, to her knowledge, no one has shown the degree to which treating sleep disorders in these patients alleviates their symptoms.

Mr. Steve Smithson, a member of the Committee, asked if Dr. Nass found that patients who were not working and receiving disability pension tend to do better than working individuals who were not receiving disability pension. Dr. Nass replied that she had not done any formal analysis of her patients, but that she recently noticed that several of her patients that had faired poorly were all working and had applied for disability. Mr. Smithson commented that it would be interesting to compare these groups to non-working, non-compensated individuals.

Dr. De Fina asked if Dr. Nass had used or thought of using methylated B12, subcutaneously. Dr. Fina commented about his foundation's research of children who were ill when vaccinated and later developed autism. He asked Dr. Nass if she saw any parallels in ill Gulf War veterans, and if perhaps receiving vaccinations in a medically compromised state could trigger chronic illnesses. Dr. Nass replied that she could not easily answer the question, because she did not know what state her patients were in when they received vaccinations. Dr. Nass then described her use of subcutaneous B12 in Cuba, adding that the expense often proves to be prohibitive. Dr. Nass stated that she typically uses sublingual B12, which is effectively absorbed in 80-90% of her patients.

Dr. Golomb echoed her belief in the importance of testing ill Gulf War veterans for B12 deficiency. She commented that the GI problems frequently experienced by ill Gulf War veterans, combined with the proton pump inhibitors often prescribed to these patients, leads to poor B12 absorption and deficiency disorders.

Dr. Nass replied that her patients and clinic staff with GI distress and gastroesophageal reflux disease (GERD) typically benefit greatly from supplements containing digestive enzymes.

At 3:35pm Chairman Binns thanked Dr. Nass and called for a break. The meeting reconvened at 3:45, when Dr. White introduced Dr. William Goldberg.

Update of VA Gulf War research

Dr. William Goldberg, VA Office of Research and Development

Dr. Goldberg announced the recent release of a Request for Application (RFA) to encourage clinical trials, including pilot studies, of treatments for ill Gulf War veterans. The submission deadline was July 15, 2009.

Dr. Steele asked if a total amount of money had been set aside for funding proposed research, and how the proposals would be assessed. Dr. Goldberg said there was no budget cap on spending, and that the reviewers would be selected ad hoc, on the basis of each proposal's content.

Dr. Steele followed up with a question about whether the proposed study design had to include chronic fatigue or fibromyalgia patients as comparison groups. Dr. Goldberg confirmed that the RFA did include that requirement. In addition, the proposed studies must include sick Gulf War veterans, and Dr. Goldberg said that the reviewers would take into consideration the inclusion and exclusion criteria used to select the study populations.

Dr. Golomb asked Dr. Goldberg to clarify how patients with fibromyalgia or CFS could qualify as control groups. Dr. Goldberg replied that studies involving treatments used in fibromyalgia or chronic fatigue patients must include a group of these patients, in addition to a group of ill Gulf War veterans and a control group.

Dr. Steele asked why the RFA was limited to clinical trials, at a time when the Department of Defense (DoD) has two mechanisms for funding treatment studies, and there has been an effort to coordinate what the VA funds with what the DoD funds. Dr. Goldberg replied that not all investigators applying for VA funding would also apply for DoD funding. He added that if he received no applications for appropriate studies, the VA would reevaluate and reissue the RFA.

Dr. Meggs asked if proposals must test specific drugs, as opposed to other treatment regimens. Dr. Goldberg said that the original aim focused on pharmaceutical trials, but that researchers were welcome to propose other forms of treatment not previously tested in ill Gulf War veterans.

Dr. Klimas commented that the VA was uniquely situated, because of its Cooperative Studies Program (CSP), to put into play a clinical trials network without a protocol in hand. Dr. Klimas proposed that this network then be used to filter phase 1 treatment ideas. Dr. Goldberg explained that the CSP allows individuals to submit a letter of intent with a concept of a trial, at which point the VA assembles an appropriate group of experts who design (or redesign) the trial. He remarked that the process is lengthy and expensive, and the resulting trials tend to be large (recruiting participants from 15-20 sites). Dr. Goldberg said that a centralized IRB exists to facilitate these projects, and that any clinical trial proposal received by the VA can be referred to this program.

Dr. Golomb commented on the historically fluctuating attitude of the VA towards researchers who were not 5/8ths VA employees, and asked what the current situation was regarding this RFA. Dr. Goldberg replied that the official rule states that 5/8ths clinicians are automatically eligible for this RFA, and non-5/8ths clinicians may apply for a waiver, but that the VA response could not be guaranteed. Dr. Goldberg advised clinicians applying for the waiver to include in their letter a brief explanation of their proposed project.

Chairman Binns remarked that because of the rapid RFA release process, the Committee was not given the opportunity to advise on the RFA, which is one of the Committee's chartered responsibilities. Chairman Binns asked Dr. Goldberg if he could explain the reasons for the rapid RFA release. Dr. Goldberg replied that a very short window of

opportunity opened up, and that the RFA was written in a matter of days. Chairman Binns then asked for any additional comments.

Dr. Nass asked where clinicians could find information about the RFA. Dr. Goldberg replied that only VA investigators could submit applications, and that the RFA was posted on the VA intranet site and sent to all of the VA research offices. Since the shift to electronic submission, the VA proposals would not be posted in the internet (and would therefore not be accessible to individuals outside of the VA system). Dr. Goldberg added that the National Institutes of Health (NIH) had rolled out the new report system replacing Computer Retrieval of Information on Scientific Projects (CRISP), and that the VA electronically funded projects were now appearing in CRISP. In this system, VA is a searchable funding institute/agency.

Chairman Binns then called for comments from the public, prior to the Committee discussion of treatments.

Public Comments

Maj. Denise Nichols mentioned her desire to alert clinicians to the existence of pertinent research findings. Maj. Nichols expressed particular concern about low testosterone levels and other hormone-related findings in Gulf War veterans. She called for greater communication and interaction between researchers and physicians in out-patient clinics. In addition, Maj. Nichols mentioned her concern with veterans' eye problems, specifically remarking that although early stages of some diseases originally manifest in the eyes, veterans must be fully service connected in order to be eligible for eye care services at the VA. Dr. Golomb expressed surprise at this, remarking that she has not had problems referring veterans for eye care evaluations at her local VA. Maj. Nichols also mentioned the importance of some of Dr. Han Kang's recent research findings, related to cardiovascular health issues. She also commented that during her time as a nurse in the Gulf War she treated many nose bleeds and gum bleeds and thought this might be significant.

Mr. Ed Bryan then addressed the Committee, stating that he would be sending a 2 page document to the Committee regarding troop exposures to oil well fires in Saudi Arabia. Mr. Bryan commented that the troops were exposed to much greater levels of oil well fire smoke than Paul 'Red' Adair and his fellow oil well firefighters. He also commented that oil well fire smoke contained thousands of chemicals. He asked the Committee to consider how Kuwaitis were being exposed to mercury, as reported by Dr. Dockery. He also called on the VA to keep closer track of the Gulf War veteran death count.

In response to Mr. Bryan's inquiry about potential sources of mercury, Dr. White commented that consuming seafood was one route of exposure. Dr. Golomb added that vaccinations could also contain mercury. Mr. Hardie remarked that some mustard agents contain mercury.

Dr. Meggs then inquired about the status of the Gulf War veteran death count. Dr. Goldberg replied that Environmental Hazards Service (EHS), where Dr. Han Kang worked, maintains and continues surveillance of a cohort of Gulf War veterans. Dr. Goldberg suggested inviting Dr. Kang to give an update. Mr. Smithson remarked that the death data could be found in the Gulf War Veterans Information System (GWVIS) Reports. Mr. Smithson commented that these reports were scheduled to come out quarterly. Dr. Kimberly Sullivan replied that these reports were disseminated to the Committee as soon as they were released. Chairman Binns recommended that the Committee staff contact Dr. Kang to inquire about the status of the GWVIS Reports. He also remarked that the other Advisory Committee on Gulf War Veterans had expressed concern with the GWVIS Reports, due to inconsistencies in data inclusion and exclusion suggestive of a computer error.

Chairman Binns then concluded the Public Comments session and called on Drs. White and Sullivan to commence the discussion of potential treatments.

Discussion of potential GWI treatments

Dr. Kimberly Sullivan opened the discussion session with a brief overview of GWI mechanisms and a summary of potential treatments and recent research (see Appendix - Presentation 7). Based on existing evidence, most hypotheses suggest a neurotoxicant-based mechanism of CNS/immune effects from acetylcholinesterase inhibitor (AChE) exposures to pesticides, anti-nerve gas pills (pyridostigmine bromide/PB) and sarin. In her presentation, Dr. Sullivan mentioned recent research on the synergistic effects of organophosphate (OP) pesticides, as well as another study that identified oxidative stress as an important mechanism in OP poisoning. She commented briefly on a CFS study that found impaired mitochondrial functioning in some patients. Dr. Sullivan also talked about mechanism and symptom-based treatments, as well as currently funded clinical trials involving some of these treatments. Mechanism-based treatments include low dose naltrexone (LDN), mifepristone, carnosine, and co-enzyme Q10 (CoQ10). Symptom-based treatments include acupuncture, biofeedback, pain medications, and nutritional supplements. Dr. Sullivan also discussed the possible utility of other new treatments and therapies, including several that could address the reduced brain white matter volumes observed in some ill Gulf War veterans.

Dr. Golomb mentioned that she was familiar with quercetin and glutathione, and commented that individualized treatment regimens involving various pharmaceutical cocktails are often used to treat mitochondrial diseases, which can manifest differently in each patient. She added that, from a purely practical standpoint, it is often difficult for clinicians and researchers to be considered for clinical trials using cocktails empirically when individual examinations of the subcomponents have not been conducted. Dr. Golomb also remarked that she had recently been told that hyperbaric oxygen therapy (HBOT) increases stem cell activity, and that further investigation into the implications of this research could be valuable.

Dr. Sullivan asked Dr. Golomb which drugs were commonly included in cocktails for mitochondrial diseases. Dr. Golomb replied that selenium, glutathione, CoQ10, alpha-lipoic acid (ALA), quercetin, B vitamins and other supplements were often used. Dr. Nass commented that she had been unimpressed with the effectiveness of these treatments in her patients. She also remarked that trying to treat reactive oxygen species involves moving ions along a series of molecules, and so combinations of substances may well be necessary for effective treatment. She added that, although promising, NADH has not been helpful. Dr. Nass said that the Sinatra solution (300-3000mg/day) was possibly helpful for clear mitochondrial disorders, but that this treatment was very expensive.

Dr. Klimas commented on an impressive placebo controlled study of CoQ10 in exercise-challenged CFS patients she had learned about at a recent CFS conference in Japan. She added that the beneficial effects observed in patients given CoQ10 were not present in patients given vitamin C, glutathione or vitamin E.

Dr. Klimas then suggested a methodological approach to treating ill Gulf War veterans, based on her knowledge of CFS and common symptoms or suspected mechanisms of GWI. With regard to sleep problems, Dr. Klimas recommended 3 approaches: pain management treatments, CPAP, and slow wave sleep inducers (gamma-hydroxybutyric acid and mirtazapine). Dr. Klimas commented on several useful studies of autonomic dysfunction in CFS, including one that involved an orthostatic challenge and response. She remarked that outcome measures must look at biological and functional outcomes, not just quality of life. Dr. Klimas also spoke about studies assessing mitochondrial dysfunction, noting that no clinical trials using mitogen (alpha-1 agonist) have been conducted, despite its common use by clinicians treating chronic fatigue patients. Dr. Klimas then spoke about studies of impaired immune functioning in patients with CFS. She mentioned that Ampligen is currently in phase 3 clinical trials for CFS and discussed her phase 1 ex-vivo cell expansion research involving the enhancement of cytolytic T cell and NK cell function. Dr. Klimas remarked that in this study, down-regulating these patients' pro-inflammatory expression yielded almost immediate cognitive improvement. She asserted that pro-inflammatory cytokine inhibitors (e.g. TNF inhibitors) are an appropriate target therapy for illnesses like CFS and GWI, though she did warn of potential side-effects. Dr. Klimas also mentioned that in a subset of patients with CFS, viruses repeatedly become reactivated, and that antiviral medications have shown to be promising in several small placebo-control studies of these patients. Dr. Klimas remarked that viral reactivation could also be a possible mechanism of GWI. She then discussed neuroendocrine CFS research. She spoke about two interventions declared failures, in her opinion prematurely. Stephen Strauss concluded early on that, despite evoking clinical improvement in CFS patients, treating them with prednisone was not worth the risk of dependency. The other reported "failure" was a growth hormone clinical trial conducted in Belgium. In this study of 18 subjects, 8 returned to work after treatment but the author concluded that the intervention was a failure based on a quality of life (QOL) instrument, which Dr. Klimas did not find sufficient as a primary outcome variable.

Dr. Nettleman remarked that she believes strongly that quality of life should be included as an outcome variable in these studies. Dr. Klimas replied that many of these chronically

ill patients will not see their limit, and that she also believes actual quality of life improvements are not always accurately measured by QOL instruments. Dr. Golomb added that multi-item QOL measures inherently weight different factors that might not all be relevant to a given individual's illness. Dr. Golomb supports single-item self-report measures because the patient then controls the weighting, according to their individual experience. Dr. Buchwald added that fatigue is multi-component, and can be measured in various ways. She prefers one or two visual analog scales (as opposed to multi-component scales), but believes that the global wellbeing scale can be effective. Dr. Nettleman emphasized the importance of well-designed studies that will answer the research questions asked. She also remarked that researchers need to be able to accept failure and be able to move forward after a hypothesis has been rigorously tested.

Dr. Klimas then asked the Committee how inclusion and exclusion criteria were used, and how the dilemma of subgrouping was dealt with, in Gulf War Illness research. Dr. Nettleman replied that rigid categorization poses a challenge, and that generalizing should only be done if the recommended treatment will be harmless to the greater population.

Dr. Meggs commented that numerous diseases manifest differently across individuals, and that only understanding the pathophysiology will reveal a common therapy. Dr. Golomb remarked that an illness with a common pathophysiology may need to be treated according to individualized regimens, since different subgroups of a given population often respond differently to particular treatments.

Dr. Bach proposed approaching the problem with "yes or no" questions. Drawing from his own research, he stated that one possible route to explore would involve asking if coagulation is involved in GWI. Dr. Bach then spoke about potential interventions, remarking that he shies away from anticoagulants, and that he believes more productive interventions should be pursued (e.g. anti-thrombotic agents or statins). He then asked the Committee for feedback. Dr. Nass replied that she knows of several people who developed antiphospholipid antibodies after receiving the anthrax vaccine. She suspected that many different parts of the clotting pathway may be affected (in different individuals). She asked Dr. Bach how he would check for clotting disorders. Dr. Bach replied that he would look at coagulation end-products. He stated that although etiology may be complicated the outcomes were not.

Dr. Buchwald commented that GWI is one of many similar syndromes, and that she felt it would be advantageous to consider the final common pathway shared by these diseases. She also commented on commonalities in altered central nervous system processing in fibromyalgia and chronic fatigue patients. Dr. Golomb cautioned that peripheral processes can affect central functioning, and that the basis of these chronic syndromes is still unknown. Dr. Buchwald remarked that most current evidence suggests that GWI originates from central nervous system dysfunction. Dr. De Fina agreed with Dr. Buchwald that the mechanisms involved in many of these illnesses are CNS-based. Dr. De Fina has conducted studies in comatose veterans using imaging neuromarkers (quantitative electroencephalography, neurospectroscopy, magnetoencephalography) to

look at changes in the brain's electrical and chemical systems which, if stabilized, improve patient functioning.

Chairman Binns concluded the meeting at 5:30pm, after reading two statements submitted by ill Gulf War veterans. Julie Mock, who suffers from GWI and multiple sclerosis, stated that she has benefitted from treatment with low-dose naltrexone (LDN), which is inexpensive and has alleviated her chronic musculoskeletal pain. She added that her night sweats have become less severe and that her stamina has improved since beginning this treatment. Another Gulf War veteran, Kirt Love, told Chairman Binns that he has been trying to reduce ill veterans' intake of sugar and high fructose corn syrup. Anecdotally, he has found that moderate crystalline fructose, unlike processed cane sugars, does not spike blood sugar levels and cause characteristic symptoms such as shaking. Mr. Love would like to see further research into this and other dietary approaches for Gulf War illness.

DAY 2

Chairman Binns called the second day of the meeting to session at 8:40am. Dr. White then introduced the first speaker, Dr. Marney Naeser.

Potential treatment for cognitive dysfunction using transcranial laser/light emitting diodes

Dr. Margaret Naeser, VA Boston Healthcare System

Dr. Naeser provided on overview of the therapeutic use and cellular effects of lasers. She then discussed several studies that used light emitting diodes (LEDs) or transcranial laser therapy to treat cognitive dysfunction, fibromyalgia, carpel tunnel syndrome, tinnitus, stroke and other disorders (see Appendix – Presentation 8). She explained that some of the effects that can be elicited by low level laser therapy (LLLT) include increased ATP production, anti-inflammatory effects and pain alleviation (via serotonin activation). As explained by Dr. Naeser, LLLT can be applied to acupuncture points or any surface area of the body, as well as intravenously.

Dr. Golomb asked what beneficial effects were observed in the German studies involving intravenous blood irradiation and laser acupuncture sessions. Dr. Naeser replied that the platelets in these patients clumped less, and that she could reexamine the paper (published in German) by Dr. T. E. Wieden for further specifics.

Dr. Meggs asked how treatment with non-coherent light (e.g. infrared sauna) compares to coherent (i.e. laser) light therapy. Dr. Naeser replied that she knows of no studies directly comparing these two forms of light therapy. She referred Dr. Meggs to the monthly list of abstracts of laser studies compiled by James Carroll on Thor Laser's website.

Dr. White asked if it is possible to determine which patients would need long-term LLLT treatments and which patients might experience long-term benefits from a single treatment or finite series of treatments. Dr. Naeser replied that in several studies of carpel tunnel syndrome involving 12 or 15 treatments, less than 10% of patients experienced regression after the final treatment. She believes that disorders involving the central nervous system may require more long-term treatment, but further research is underway, including studies investigating diode implantation.

Dr. Golomb commented on a trial in a nursing home of elderly patients whose cognitive function was improved by exposure to bright lights in the rooms.

Dr. Naeser concluded her presentation by briefly reviewing several case studies of LLLT and LED therapy for wound treatment and cancer patients.

Chairman Binns thanked Dr. Naeser for her presentation. He then stated that he used to work in the field of ultrasound imaging and mentioned that his former partner is currently working with low level magnetic energy to treat peripheral neuropathies.

Dr. White then introduced the next speaker, Dr. Dedra Buchwald.

Current therapies for fibromyalgia

Dr. Dedra Buchwald, Research Advisory Committee on Gulf War Illnesses

Before giving her scheduled talk on fibromyalgia treatments, Dr. Buchwald spoke about issues to be considered when measuring fatigue, many of which are relevant to studying and assessing pain, neurocognitive functioning, and other symptoms or syndromes (see Appendix – Presentation 9). In speaking about the multi-faceted nature of fatigue and other symptoms, Dr. Buchwald specifically spoke about behavior, perception, mechanisms, and context.

Dr. Golomb remarked that sometimes if a subjective measurement doesn't track with the objective measurement it may mean that the appropriate objective measurement has not been identified. She also asked whether Dr. Buchwald thought it would be useful to use objective measures in conditions characterized by subjectively reported symptoms. Dr. Buchwald replied that she agreed with Dr. Golomb's first point, and that no perfect answer exists for her question. She commented that, if pertinent, objective measures should be included.

Dr. Klimas asked if the Gulf War research community has reached any consensus about using standard instruments so that study results can be compared. Dr. Buchwald replied it is not sufficient to use an instrument simply because it is widely accepted. She added that it is best to use a measure that has been validated, or to augment one instrument with another robust instrument. Dr. Klimas then mentioned a paper by William Reeves that listed the instruments different CFS researchers were using, along with the pros and cons of each. Dr. Buchwald added that another useful resource was the National Institute of Health's (NIH's) Promise

Initiative, which assigned experts in a wide range of domains to select the best short measures for use in clinical studies.

Dr. Buchwald then gave a presentation on the clinical features of and treatment approaches to fibromyalgia (see Appendix – Presentation 10). In her presentation she discussed diagnostic criteria, co-occurring conditions, complexities of patient care, behavioral management strategies, pharmacological interventions and augmented care.

LTC Knox asked Dr. Buchwald about catastrophic beliefs, and whether they are necessarily precipitated by catastrophic events. Dr. Buchwald replied that catastrophic thinking is not a symptom or characteristic of traumatic stress disorder. She stated that, in her opinion, catastrophic thinking is a personality trait.

Dr. Golomb commented on a recent presentation she saw at a meeting of the American Psychosomatic Medicine Society, where researchers revealed that among doctors and family members of sick individuals, some diseases (e.g. heart disease) were perceived in an honorable light, whereas individuals with multi-symptom illnesses tend to be viewed with an element of contempt by practitioners and family members. Dr. Golomb called for greater interventions to make family and physicians aware of these inferior perceptions of people living with multi-symptom illnesses.

Dr. Golomb then addressed Dr. Buchwald's comment on psychiatric comorbidity, remarking that she believes that the rate of psychiatric conditions is not elevated in fibromyalgia patients. Dr. Buchwald agreed that fibromyalgia patients did not experience increased rates of psychiatric conditions compared to individuals with other chronic diseases, but that fibromyalgia patients did have higher rates of psychiatric conditions compared to the general population.

In response to Dr. Golomb's earlier comment, Dr. Buchwald mentioned a study in which patients reported that being given a diagnostic label was the single most enabling event in the course of their illness.

Dr. Steele asked about the greatest pharmacological response rate in fibromyalgia patients. Dr. Buchwald replied that the most effective drugs to date elicited a 30-40% response rate. Dr. Steele asked if there were any predictors of who would respond to treatment versus who would not. Dr. Buchwald replied that she was not aware of any.

Dr. Meggs asked if any data exist to determine whether the increased prevalence of fibromyalgia is due in any part to increased recognition and diagnosis. Dr. Buchwald replied that, over time, people's diagnoses change despite consistent symptoms. Dr. Buchwald does not believe that the prevalence in fibromyalgia is actually increasing dramatically.

Maj. Nichols commented that people in the military during the Gulf War were voluntary recruits whose slogan was "without pain, there is no gain." She made the point that this population was not made up of typical citizens, and that clinicians should take into consideration the challenging lives that many Gulf War veterans had chosen to pursue. Maj.

Nichols also asked the Committee to think about low-level nerve gas exposure, depleted uranium (DU), and events and the toxic chemical exposures that occurred among the civilian population in Iran during the years preceding the Persian Gulf War.

At 11:00am Chairman Binns thanked Dr. Buchwald for her presentation and called for a 15 minute break.

After the break, Dr. White introduced the next speaker, Dr. Philip De Fina.

Innovative therapies for mild brain injuries

Dr. Philip De Fina, International Brain Research Foundation & the Kessler Institute for Rehabilitation

Dr. De Fina, a neuropsychologist and neurophysiologist, spoke about the work he is doing on disorders of consciousness due to brain injury (see Appendix – Presentation 11). His presentation focused on the use of neuromarkers, specifically functional imaging neuromarkers, to guide treatment and predict outcomes. Dr. De Fina emphasized the necessity for an individualized, multi-modal diagnostic approach. Some of the instruments used by Dr. De Fina in the evaluation phase include quantitative electroencephalography (qEEG), event-related potentials (ERP), magneto-encephalography (MEG), standardized low resolution brain electromagnetic tomography (sLORETA), magnetic resonance imaging (MRI), and near infra-red spectroscopy (NIRS). Dr. De Fina also spoke about qEEG-guided neurorehabilitation as a feasible treatment model within which various therapeutic approaches, including neurofeedback, low level electrical stimulation, and transcranial magnetic stimulation (TMS) can be integrated to improve cognitive functioning.

Dr. Meggs asked Dr. De Fina what his pharmaceutical regimen consists of. Dr. De Fina replied that it included flumazenil, naloxone, and many other pharmaceuticals and nutraceuticals to choose from. He added that he was reluctant to share exact regimens without controlled collaboration from inquiring researchers and that he was interested in collaborating with VA researchers in future studies.

Dr. O'Callaghan asked if Dr. De Fina's individualized protocols were informed by his neuromarkers. Dr. De Fina replied that they were, though the process is still evolving.

Dr. Steele asked if Dr. De Fina or his research team had done work on individuals suffering from brain diseases such as amyotrophic lateral sclerosis (ALS), rather than trauma. Dr. De Fina replied that no work had been done on ALS, though one patient with Alzheimer's Disease had been put through the same protocol used in patients with traumatic brain injury (TBI). Dr. De Fina mentioned that his group is also working on an unfunded pilot project in autistic children.

Dr. Steele asked if the results of the imaging were being used to shape the course of treatment for these patients. Dr. De Fina said they were, and that the autism patients were being treated with subcutaneous methyl-B12, HBOT, pharmaceuticals, neutraceuticals and biofeedback. Dr.

De Fina added that all patients were treated based on the metabolic and electrical changes in their brains, so that cause of illness does not necessarily determine course of treatment. He believes his paradigm could thus be applied to many other disorders.

Dr. Golomb asked if response to treatment with subcutaneous methyl-B12 depended on patients' baseline B12 levels. Dr. De Fina replied that baseline levels are not reliable indicators of deficiency, since B12 can be present but not able to be metabolized by the body.

Dr. Sullivan commented that diffuse axonal injury in mild TBI, like Gulf War Illness, is characterized by reduced white matter volume. Since Dr. De Fina has treated mild TBI, Dr. Sullivan asked him what thoughts he had on treatment regimens for ill Gulf War veterans. Dr. De Fina said that a protocol had been written up for mild TBI, but that the research had not yet been funded, so treatment had not begun. He said he would be willing to speak about the protocol further in person.

Dr. Naeser asked where the cathode and anode were placed in the transcranial direct current stimulation example Dr. De Fina used in his presentation. Dr. De Fina replied that this varied from patient to patient, according to EEG readings.

Dr. Klimas asked if Dr. De Fina used any direct or systemic measures for determining neuroinflammation. Dr. De Fina replied that he currently has no direct means of directly measuring neuroinflammation, but that he would like to use blood biomarkers to obtain that information. He added that his protocol includes using curcumin and other neutraceuticals to combat neuroinflammation.

Dr. Nass asked what the cost of the evaluation and treatment protocol is, and whether an inexpensive, abbreviated version of the protocol exists. Dr. De Fina replied that a 12 week protocol for severe disorders of consciousness costs $35,000 to $50,000 (on top of in-patient fees). He added that this was less expensive than long-term nursing home care. He recommended that qEEG and ERP (as opposed to MRS and other more costly instruments) be used to evaluate out-patients.

Dr. Golomb asked if Dr. De Fina had concerns about waking individuals too early. Dr. De Fina replied that although interrupting the acute phase following injury could be harmful to a patient, the therapeutic benefits of remaining unconscious become obsolete at a certain point in time that has yet to be determined.

Dr. Sullivan asked if Dr. De Fina could reflect on his experiences with HBOT. Dr. De Fina replied that HBOT had only been used in several severe TBI cases, and in these cases it was used in conjunction with other treatment modalities.

Dr. Nass asked if any relatively simple, cost-effective intervention exists for the large numbers of soldiers returning from the current war with TBI. Dr. De Fina stated that qEEG, ERP electrical brain mapping can be done at any DoD or VA facility in the U.S. or abroad, and that these approaches could be used to direct neurotherapies. He also stated that they could be used to differentiate between TBI and PTSD cases.

At 12:40pm Chairman Binns thanked Dr. De Fina and asked if Dr. White or Dr. Sullivan had any concluding remarks.

Dr. Sullivan thanked everyone for coming and Dr. White expressed appreciation for the innovative focus of the meeting and encouraged people to contact her or Dr. Sullivan with treatment-related suggestions.

Chairman Binns then adjourned the session after thanking Dr. Sullivan for assembling an extraordinary meeting program.