Research Advisory Committee
On
Gulf War Veterans' Illnesses

Minutes of Meeting
February 3rd & 4th, 2003

U.S. Department of Veterans Affairs
810 Vermont Ave., NW
Washington, D.C.

TABLE OF CONTENTS

ATTENDANCE RECORD

Members of the Committee in Attendance:
James Binns
Nicola Cherry
Joel Graves
Beatrice Golomb
Robert Haley
Marguerite Knox
William Meggs
Philipe Pellier
Steve Robinson
Steve Smithson
Lea Steele

Consultant to the Committee
Jack Melling

Guest Speakers:
Nelda P. Wray, MD, MPH, Chief Research & Development Officer, DVA
Hermona Soreq, PhD
Han Kang, PhD
Thomas Finley, MD
Jeffrey Phillips, Deputy Assistant Secretary, DVA

Designated Federal Officer
Laura O'Shay

Abbreviations

Most abbreviations are also defined in the text

ACh – acetylcholine, an important nerve signaling chemical

AChE – acetylcholinesterase, a key enzyme involved in breaking down and regulating acetylcholine (ACh)

AChEi – acetylcholinesterase inhibitor, a chemical that blocks the action of AChE thus leading to accumulation of ACh in the short term (However, long term effects may include depressed function of the acetylcholine system.)

AE – Aerobic Exercise

ATT – Antibiotic therapy trial

CBT – Cognitive and behavioral therapy

CCEP – Comprensive Clinical Evaluation Program

CFS – Chronic fatigue syndrome

CNS – Central nervous system (generally considered to include to the brain and spinal cord)

DAS – Deputy Assistant Secretary

DEET – an insect repellant

DFP - Diisopropylfluorophosphate, an organophosphate acetylcholinesterase inhibitor

DMDC - Defense Manpower Data Center

DoD – Department of Defense

DVA – Department of Veterans Affairs

EPA – Environmental Protection Agency

ET – Exercise therapy

EBT- Exercise and cognitive/behavioral therapy

FTE – Full Time Equivalent (e.g. the number of FTEs assigned to a project or facility reflects the number of full time hires or personnel for whom staffing has been allocated)

FM – fibromyalgia

fMRI – functional magnetic resonance imaging (permits following brain images and viewing regional activity in the brain over time, associated with certain tasks or mental processes)

GW: Gulf War

GWI: Gulf War illnesses

GWV: Gulf War veteran(s)

GWVIS – Gulf War Veterans Information Service

HSRD or HSR&D – Health Services Research and Development

IOM – Institute of Medicine

LOI – Letter of Intent (e.g., intent to submit a proposal, in response to an RFP)

MD – Doctor of medicine

MRI – Magnetic Resonance Imaging

mRNA: Messenger ribonucleic acid

MUS – Medically unexplained symptoms

MVA – Motor vehicle accident

NAS – National Academy of Sciences

NIH – National Institutes of Health
OMB – Office of Management and Budget
ONR – Office of Naval Research
OP – organophosphate, a class of acetylcholinesterase inhibiting chemicals that include organophosphate nerve agents (like sarin, soman, tabun, VX) and organophosphate pesticides (including, among many others, chlorpyrifos, diazinon)
PB - Pyridostigmine bromide
PCS – Physical Component Summary, of the SF-36 instrument
PhD – Doctor of Philosophy
PI – Principal investigator
PON – Paraoxonase, an enzyme involved in metabolizing (or ridding the body of) organophosphate acetylcholinesterase inhibitors
PTSD – Post traumatic stress disorder
RFP – Request for Proposal
RR - Risk ratio
VA – Veterans Affairs
VAMC – VA Medical Center
VISN – A regional grouping of Veterans Affairs Medical Centers (e.g., VISN 22 includes VA Medical Centers in Southern California, such as the San Diego, Long Beach, and West Los Angeles VA Medical Centers).
VSO – Veterans Service Organization
WRIISC - War-Related Illness and Injury Study Center

Research Advisory Committee on Gulf War Veterans Illnesses
Committee Meeting
February 3-4, 2003
Department of Veterans Affairs
810 Vermont Avenue, NW
Washington, DC

AGENDA
February 3, 2002
Room 830

Time	**Topic**	**Speaker(s)**
8:00 a.m.	Introductory Remarks	Mr. James Binns
8:15 a.m.	Major VA Studies	Dr. Nelda Wray, Chief, VA R&D, and investigators
9:00 a.m.	Antibiotic Therapy Trial (ABT)	
9:20 a.m.	Discussion/Comments	
9:35 a.m.	Exercise Behavior Therapy Trial (EBT)	Dr. Nelda Wray
9:55 a.m.	Discussion	
10:10 a.m.	Break	
9:50 a.m.	ALS study	Dr. Nelda Wray
10:45 a.m.	Discussion	
10:20 a.m.	Phase III, National Gulf War Veterans' Survey	Dr. Nelda Wray
11:05 a.m.	New Research Update	Dr. Beatrice Golomb
11:25 a.m.	Discussion	
11:45 a.m.	Lunch	
1:30 p.m.	Research at Washington, D.C., War-Related Illness and Injury Study Center (WRIISC)	Dr. Han Kang, Director, Washington, D.C. WRIISC
1:45 p.m.	Discussion	
2:00 p.m.	Research at New Jersey WRIISC	Dr. Tom Finley, Director of Research, NJ WRIISC
2:30 p.m.	Discussion	
2:45 p.m.	Break	
3:10 p.m.	EN101 Antisense Drug	Dr. Hermona Soreq, Hebrew Univ. of Jerusalem
3:2 p.m.	Discussion	

3:40 p.m.	Treatment Research Concepts	Dr. Lea Steele
4:10 p.m.	Discussion	
5:15 p.m.	VA actions to publicize new initiatives	Jeffrey Phillips, DAS Public Affairs
5:30 p.m.	Public Comments	
6:15 p.m.	Adjourn	

AGENDA
February 4, 2003
Room 230

Time	**Topic**	**Speaker(s)**
8:00 a.m.	Mechanism Research Concepts	Dr. Beatrice Golomb
8:45 a.m.	Mechanism Research	Dr. Hermona Soreq
9:15 a.m.	Discussion	
10:15 a.m.	Break	
10:30 a.m.	Vaccine Research Concepts	Dr. Jack Melling
11:00 a.m.	Discussion	
11:30 a.m.	Lunch	
12:30 p.m.	Recommendations	Mr. James Binns
1:45 p.m.	Japanese conference report	Dr. William Meggs
2:00 p.m.	Break	
2:15 p.m.	GWVIS report	Mr. Steve Robinson, Dr. Robert Haley
2:45 p.m.	Committee 2003 Work Plan	Mr. James Binns
3:30 p.m.	Public Comments	
4:00 p.m.	Adjourn	

1.

Introductory Remarks James Binns, Jr., Chairman

The meeting was called to order at 8:00 am by Chairman James Binns. He welcomed guests and members of the Committee. Mr. Binns observed that following its first meeting in April, 2002, the Committee issued its initial report in June, 2002, which challenged traditional government thinking regarding Gulf War veterans illnesses. He observed that important new research has been published during the past eight months that support the positions taken by the Committee. He noted that the Committee members could feel good that their work has been proven correct, but sick veterans still do not feel good. What they have gained during this time is hope. They have gained the hope that researchers are now beginning to understand their illness better and to believe in their symptoms. They have gained one more thing: they are not alone. They are no longer considered to be the stragglers from a forgotten war, but the advance party for the rest of us. In the course of researching the mechanisms and possible treatments for Gulf War illnesses, we can also learn how to improve protection against future chemical attack for troops in the field and civilians at home.

Mr. Binns introduced the first guest speaker, Dr. Nelda Wray, MPH, MD, the new Chief Research & Development Officer for the Department of Veterans' Affairs. Dr. Wray gave an update on several large VA/DoD cooperative multi-million dollar research projects.

2.

Antibiotic Therapy Trial (ABT): Doxycycline Treatment of Gulf War Veterans' Illnesses: A VA/DoD Cooperative Study
Presenter: Dr. Nelda Wray, Chief, VA R&D, and Investigators.

(See **Appendix A** for the corresponding PowerPoint presentation.)

The goal was to determine if doxycycline treatment for one year would significantly improve the functional status and/or chronic symptoms of ill Gulf War veterans who test positive for mycoplasma. See attached Appendix A regarding the content of the talk, which relayed the methods and findings of the study, which are also available in the published literature.

Briefly, ill veterans who tested positive for mycoplasma by PCR (polymerase chain reaction) were randomized to receive the antibiotic doxycycline or a placebo for one year of treatment. Veterans were eligible from a health perspective if they reported at least two of three symptoms, of fatigue, musculoskeletal pain, and cognitive problems; if these symptoms were chronic, persisting for at least six months; if the symptoms began after August of 1990, and thus were not present prior to participation in the Gulf War; and if they had a score of less than 40 on the Physical Component Summary (PCS) of the SF-36 instrument. Among 2712 screened veterans, 2134 met symptom inclusion criteria, of whom 1565 had a score of less than 40 on the PCS. Of 1387 screened ill veterans, 541 (39%) tested positive for mycoplasma. Ultimately, 491 were randomized, with 411 completing the PCS at baseline and 12 months. The primary endpoint of the study was

the proportion of subjects experiencing a 7 point or greater increase in the PCS at 12 months. Assessments were performed at 3, 6, 9, 12, and 18 months; with PCR for mycoplasma at 6, 12, and 18 months. Initially 40% of tested veterans tested positive for mycoplasma. No benefit was found in the designated primary assessment at 12 months.

Discussion:

Dr. Golomb noted that the study was positive at the three month follow-up, with significantly greater improvement in the antibiotic treatment group relative to the placebo group ($p < .01$), but the apparent benefit was lost with continued treatment. She expressed concern about the study finding that a population (of ill Gulf War veterans) with a 40% mycoplasma positivity at outset, in which that 40% were selected for study, could convert from 100% positivity to 10% positivity by study end in both placebo and treatment groups. One might expect that they would retain at least the 40% overall positivity rate, even if positive status reflected merely a nonstable, fluctuating 40% of ill veterans who were positive at any point in time.

Dr. Golomb also expressed concern about use of the threshold change in PCS score as the primary outcome, in contrast to the usual approach of assessing whether there is a significant difference in mean scores. Indeed, the threshold was set fairly high, higher than the mean change in score on the exercise cognitive-behavioral therapy trial that had been deemed a positive finding. (Having determined whether there is a mean difference, one can subsequently assess how clinically meaningful the effect is, or whether it appears to be confined to a subset, etc.)

Dr. Wray stated that this magnitude of difference was selected as that required for an individual subject to be reliably be aware of a quality of life improvement.

Dr. Golomb inquired as to the mean difference in PCS score between the antibiotic treatment group and the placebo group at the designated 12-month comparison time. She was told by the investigators that the PCS score was on average one point better in the antibiotic than the placebo group (a difference that was not statistically significant). (See discussion of EBT study.)

Dr. Meggs commented that after one year of doxycycline, if it doesn't seem to help these people, we should move on and look in other areas.

Mr. Graves remarked that a lot of money was expended for a study he felt might have been predicted to be negative.

Dr. Pellier asked if anyone had looked at real mycoplasma infections.

Mr. Robinson questioned whether subjects had been able to try the ABT (antibiotic treatment) and EBT (Exercise and Cognitive and Behavioral Therapy) trials in combination, and was told that subjects could only enroll in one protocol at a time. He also requested confirmation that the study period had been April 1999 to Sept. 2001.

Dr. Nass, from the public, said that she had been told by a study investigator that the study was actually a failure because of high crossover, with some antibiotic subjects discontinuing their medications , therefore there hadn't been a proper adherence to the test protocol.

Dr. Steele commented that when Mycoplasma were subsetted by type of mycoplasma – *M fermentans, M pneumoniae, M genitalia* -- the same percentage of each group appeared to experience mycoplasma eradication, suggesting that the treatment was not specific to the species.

Dr. Haley posited that there could have been a regression toward the mean to account for the results of no difference following the three month marker period.
Mr. Graves said that soldiers in combat were more ill than those in support units and asked if they further divided the group according to their physical location.
He was told that they did not. Mr. Graves inquired why that had not been done.
Dr. Wray stated that following the three month visit, both active treatment and control populations came together so it was senseless to further divide the groups.
Dr. Melling commented that the study should lay the ghost to rest, but inquired why and how subjects developed mycoplasma positivity in the first place?
Mr. Smithson asked whether there were long term follow-up benefits after the 12 months test period, and was told there were not.
Dr. Meggs said that maybe 40% of the general population are infectious carriers.
Dr. Golomb cited prior studies, such as that by Dr. Daryl See, showing mycoplasma positivity in ~10% of healthy controls, 10% of persons with chronic fatigue without immunodeficiency markers, and as recollection serves, around 40% of those with HIV, and a similar or higher fraction of those with chronic fatigue syndrome with immunodeficiency markers, as well as persons with rheumatoid arthritis, which some have considered possibly a mycoplasma-mediated disease. (Long-term antibiotic treatment trials have been favorable in persons who are recent converters to positive serological status for rheumatoid factor, with actual arrest of progression of disease and apparent "cure" occurring more commonly in the antibiotic than the placebo group.)
Dr. Haley said that he worried about false positives, especially during the winter.
Dr. Golomb asked what happened to the initial plan to use a set of laboratories for the mycoplasma testing, to provide for a reliability mechanism.
Dr. Wray responded that there were problems getting cross-laboratory comparability, and ultimately a single laboratory was chosen.
[Post-meeting follow-up: Following the meeting, Dr. Golomb spoke with Dr. Garth Nicolson, who originated the mycoplasma theory of Gulf War illness. Dr. Nicolson had been one of the initial intended test sites. Dr. Nicolson stated that the samples sent were degraded, by a variety of tests he performs for sample integrity. He stated that samples are very sensitive to collection and handling procedures, and that he had advised what steps were needed (e.g. prevention of freeze-thaw cycles), but that these steps were not undertaken. He stated that the samples sent for mycoplasma testing were untestable.]

3

Exercise Behavior Therapy Trial (EBT): A Multi-center Trial of Cognitive Behavioral Therapy and Aerobic Exercise for Gulf War Veterans' Illnesses: A Veterans Affairs/Department of Defense Cooperative Study
Presenter: Nelda P. Wray, MD, MPH Chief Research & Development Officer

(See **Appendix B** for the PowerPoint presentation. Note that details of this study are available in the published literature.)

Dr. Wray gave credit to the study's co-chairs: Dr. Sam Donta, Dr. Charles Engel and Dr. Daniel Clauw**,** for their work on the project.

She noted that symptoms in some of the ill veterans resembled chronic fatigue syndrome (CFS) and fibromyalgia (FM) and that cognitive behavioral therapy (CBT) and aerobic exercise (AE) has been shown to be effect in the treatment of symptoms of those disorders in both military and civilian populations.

The stated goal of the study was to determine if CBT or AE would improve the functional status and/or the chronic symptoms expressed by ill Gulf War veterans. Details of this presentation track the published findings, and will not be reproduced in detail here. Inclusion criteria symptoms were the same as those for the antibiotic treatment trial, symptoms lasting at least 6 months in two of three categories of fatigue, musculoskeletal pain, and cognition; coupled with a PCS score of less than 40. Twelve weeks of treatment were given with cognitive/behavioral therapy (12 group sessions lasting 60-90 minutes with groups of 3-8 subjects); and aerobic exercise, weekly one hour sessions for 12 weeks to increase activity, with subjects instructed to exercise at least 2-3 times a week during treatment and follow-up. Assessments were performed at 3, 6, and 12 months, with the primary endpoint being the proportion of subjects who showed at least a 7 point increase in the PCS. (Secondary health outcomes included fatigue (Multidimensional Fatigue Inventory), cognition (Cognitive Failures questionnaire), pain (McGill Pain Questionnaire), distress, and mental health functioning (improvement in score on the Mental Component Summary, or MCS, of the SF-36V. Of 2793 veterans interviewed, 1448 had a PCS score > 40; 253 were not interested in participating. 1092 were randomized, with 266 assigned to CBT+AE, 269 to AE, 86 to CBT and 271 to usual care (control). 998 (91%) completed the study. Regarding the primary outcome, the proportion who showed more than a 7 point increase in the PCS at 12 months was 18.4% in the CBT + AE group; and 18.5%, 11.7%, and 11.5% in the CBT, AE, and usual care groups, respectively. Those receiving CBT with or without AE experienced benefit. AE did not lead to significant benefit as indexed by this outcome, though AE looked favorable from vantages of key secondary endpoints.

Discussion:
Mr. Smithson asked what kind of long-term follow-up benefits were provided by the study. He was told that there were none.

Dr. Steele commented that subjects who were taking anti-depressant medications were those who showed a significant improvement from CBT. CBT has been shown in other studies to have benefits for subjects with mild depression.

Dr. Cherry asked information about the placebo group (placebo intervention) and was told there was no placebo group. (The control group was confined to the usual care group.)

Dr. Steele asked if there were any reported differences between the different sites where the studies took place?

Dr. Wray stated that the hope was to build exercise into their way of life; CBT is touted as a therapy trying to change thinking and behavior.

Mr. Graves said that ill people are more prone to depression because they are sick and that the two studies did not address anything new. He said that one would expect the slight changes and that what is really needed are treatments. He said that these studies are just validating what is already known about the therapies.

Dr. Golomb asked what the average magnitude of the difference in PCS score was between the treatment group and the control group. The intervention group performed better by a mean of one point. She asked for confirmation that the mean difference in treatment and control group was in fact the same -- one point difference -- as occurred in the antibiotic treatment trial. This was confirmed. This mean difference was significant in the EBT but not the AE trial (separate from the question of the 7-point difference). This can be explained by the fact that twice as many subjects were enrolled in the EBT trial, so that trial had substantially greater power to show significance for the same magnitude of mean benefit .

4.

Amyotrophic Lateral Sclerosis (ALS) Among Gulf War Veterans
Presenter: Nelda P. Wray, MD, MPH Chief Research & Development Officer

PI: Ronnie Horner, PhD, Durham VAMC
Dr. Wray summarized from the original with the permission of the author.
(See **Appendix C** for the PowerPoint presentation)

Dr. Wray reported on a cooperative research project between the DoD and the VA conducted during March 2000 through November 2001 in response to a concern in the Spring of 1999 regarding a possible increased rate of ALS in Gulf War veterans. The expressed primary goal of the study was to compare the incidence of ALS in deployed veterans with the incidence in non-deployed veterans.

Added Background (adapted from Harrison's Textbook of Internal Medicine): ALS is a fatal neurological disease that destroys both upper and lower motor neurons. Upper motor neurons are neurons in layer 5 of the"motor cortex" area of the cerebral cortex that control movement, and that synapse on lower motor neurons, directly or through interneurons. Lower motor neurons are neurons (called anterior horn cells) are neurons in the spinal cord that synapse directly on muscle cells; or analogous brainstem neurons that synapse on "bulbar" muscles that control speech and swallowing. As the neurons die, muscles weaken and shrink, causing weakness and atrophy. Initially, symptoms may be asymmetric, and either upper or lower motor neuron symptoms may predominate. Lower motor neuron symptoms include twitching of muscles ("fasciculation"), that may occur particularly early in the illness; and weakness with hand extension, breathing, or chewing, swallowing, or movements of the face and tongue may occur. Cramping with initiation of movement may occur. With upper motor neuron (corticospinal) involvement, the tendon reflexes are hyperactive, and there may be spastic resistance to passive movements. Muscle stiffness may be out of proportion to weakness; and "pseudobulbar affect" may occur from exaggeration of the motor expressions of emotion, such as weeping or laughing. Later, both upper and lower motor neurons are both affected (indeed, this has become

a World Federation of Neurology criterion for ALS). Initially, virtually any muscle group may be the first to show symptoms. With time, more and more muscles become involved, so that ultimately the disease appears symmetric. For a diagnosis of ALS to be given, there must be simultaneous upper and lower motor neuron involvement with progressive weakness, and the exclusion of all alternative diagnoses. ALS is considered "possible", "probable", or "definite" according to whether one site, two sites, or three or four sites among the following four are affected: Bulbar, cervical, thoracic, and lumbosacral motor neurons.

The illness progresses relentlessly, generally leading to death from respiratory paralysis, with median survival from 3-5 years. There are rare reports of stabilization or regression. In most societies the incidence is 1-3 per 100,000, with a prevalence of 3-5 per 100,000 (not age adjusted). Males are more frequently affected than females in the U.S. 5-10% of cases are inherited as an autosomal dominant trait.

Study Population
The targeted population was all service members, including activated Reserve and National Guard, who served on active duty for at least one month during August 1990-July 1991. Cases were identified nationwide.

Active Methods
-VA & DoD hospitalization databases
-VA & DoD ambulatory care databases
-VA & DoD pharmacy databases (prescriptions for Riluzole)
-VA & DoD disability benefits databases

Passive Methods
-National toll-free hotline number (DIAL-ALS)
-ALS Association website
-National media campaign
-Mailings to all 11,000 members of American Academy of Neurology
-Mailings to all neurologists working for VA Medical Centers
-Mailings to members of Veterans' Service Organizations

Confirmation of Disease Status
-Verification by review of medical records or death certificates
    -two neurologists reviewed each case
-Disagreement resolved by neurological exams (4 cases)
-In-person interviews: medical history and environmental exposures

516 Suspected ALS Cases
-Able to locate & contact 476 suspected cases (92% of 516)
-163 suspected cases were eligible for study (34% of 476)
    -279 suspected cases did not have diagnosis of ALS confirmed
    -28 suspected cases not eligible for other reasons (diagnosis before 8/1/90 or not on active duty Gulf War)

-6 suspected cases refused participation

Results of Verification of 163 Suspected ALS Cases

-107 confirmed ALS cases (66% of 163)
-82 confirmed cases verified with medical records
-25 confirmed cases verified with death certificates
-24 suspected cases refused participation (5 cases refused for fear of losing benefits; most refusals due to severity of advanced ALS)
-15 suspected cases did not have diagnosis of ALS
-17 suspected cases medical records could not be obtained

Annual Incidence Rate of ALS

-Rate of ALS expressed as number of confirmed ALS cases per year per 100,000 persons
-Rates age-adjusted
-Compared to non-deployed ALS cases, Gulf War ALS cases were:
-younger
-more likely to be Caucasian
-more likely to be Reserve/National Guard
-more likely to be Army
-Overall rate 0.43 cases per 100.000
-107 cases in 2,482,333 veterans
-Gulf War veterans 0.67 cases per 100,000
-40 cases in 696,118 Gulf War veterans
-Non-deployed veterans 0.35 cases per 100,000
-57 cases in 1,786,215 in ND veterans
-Risk ratio: Gulf War veterans compared to non-deployed veterans: 1.92 (95% CI=1.29, 2.84)
-Risk Ratio in:
- Gulf War Air Force troops vs. ND Air Force: RR=2.68
- Gulf War Air Force troops vs. ND Army troops: RR=2.04
-Risk Ratio of Gulf War veterans, compared to non-deployed veterans, was recalculated three different ways
-using stricter diagnostic criteria
-including only cases with symptom onset after July 31, 1991
-using self-reported deployment status
-Each of these analyses found significantly increased risk in Gulf War veterans

VA Response to ALS Study

In December of 2001, Secretary Principi gave service connection for ALS to veterans who served in Operations Desert Shield and Storm. The VA contacted Gulf War veterans in the study to help expedite claims for disability benefits.

VA Continues to Investigate ALS

The VA is reviewing the subject interviews of medical history and environmental exposures, and will report on the results of this review. The VA is continuing to assess cases of ALS and controls diagnosed after August 1, 2000. A twenty year study of

incidence and mortality due to ALS in all veterans in Texas has commenced (Houston VAMC; started in 2001). The National Registry of Veterans with ALS is undertaking identification and interviews of all ALS cases diagnosed in VA hospitals (Durham VAMC; started in 2002).

Determination of Deployment Status
The determination of Gulf War status was based upon records of the Defense Manpower Data Center (DMDC). There has been an effort to reconcile the records of the self-reported cases and those from the official DMDC records in order to have a single set of case statistics.

Discussion:
Dr. Haley asked what were the number effect estimates in the Army and the Navy and was told that the risk was elevated in both.

Dr. Meggs mentioned that elevated rates of ALS have been reported among pilots.

Dr. Haley asked how many came home from the war with Gulf War illnesses (GWI) before they developed ALS.

Dr. Wray said she would be interested in conducting those interviews to find out.

Mr. Graves asked if they have done a study to see how many were actually Army aviators and was told that they have not.

Dr. Cherry asked if there had been any genetic work done in the study and was told that they are underway and that six cases had a family history of ALS.

Dr. Cherry asked if blood samples were being taken to look for genetic markers; she was told the answer was no.

Dr. Wray mentioned that the VA was putting extra $300,000 funding in to the Research Enhancement Award Program (REAP), according to which if a group has 3 or more studies, the VA will provide money to encourage scientists to bring in more people to be able to create a center to compete for larger grants.

5.

National Health Survey of Gulf War Era Veteran's and Their Families Phase III
Presenter: Nelda P. Wray, MD, MPH Chief Research & Development Officer

(See **Appendix D** for the original presentation.)

The purpose of the study was to compare the health status of a representative sample of 15,000 Gulf War (GW) veterans and 15,000 non-deployed veterans using mail and telephone surveys. Compared to non-deployed veterans, Gulf War veterans reported increased frequency of each of 48 queried symptoms; and increased frequency of hospitalizations and clinic visits in the prior 12 months.

The study sought to determine the prevalence of several illnesses in a representative sub-sample of veterans and their families through comprehensive medical and psychiatric examinations, in a random selection of veterans who had participated in Phases I and II of the National Health Survey. 4879 subjects were invited to participate, with evaluations including general physical, neurological, and gynecological examinations; structured psychiatric interviews; standardized neuropsychological testing; standard blood and urine tests; pulmonary function tests; and nerve conduction studies. 1061 Gulf War veterans (53% response) and 1128 nondeployed veterans (39% response) participated.

Gulf War veterans were significantly more likely to have chronic fatigue syndrome (1.6% vs 0.1%, adjusted $p < 0.0001$) or fibromyalgia (2.0 vs 1.2%, adjusted $p = 0.04$; and had significantly lower PCS scores on the FS-36, though the difference was not considered to be clinically significant (49.3 vs. 50.8, adjusted $p < 0.0001$). They were less likely to have peripheral neuropathy (2.8% vs. 4.0%, adjusted $p = 0.04$). (However they were on average 2 years younger; and persons with diabetes, medications, and significant alcohol usage, the groups most likely to develop neuropathy, may have selected out from deployment.) They were also more likely to have dyspepsia (9.1% vs 6.0%, $p = 0.01$) and "Group 2" skin conditions (34.6% vs 26.8%, adjusted $p = 0.02$), with two specific skin conditions individually significantly different, namely atopic dermatitis and warts. Hypertension was not significantly different in the groups following adjustment. Cognitive dysfunction was not significantly different between Gulf War veterans and controls. PTSD rates were greater (8.0 vs 2.8%, $p = 0.0001$); and the MCS (Mental Component Summary) score of SF-36 was lower (50.0 vs 53.7, p = 0.%001). Alcohol dependence and major depression were not significantly different following adjustment. However anxiety disorders (5.8% vs 2.4%, $p = 0.002$); bipolar disorder (1.0% vs <0.1%, $p < 0.0001$); and one or more mental disorders (29.1% vs 17.1%, $p < 0.0001$) were more common in Gulf War veterans.
Spouses: There were no significant differences in rates of primary and secondary outcomes spouses of Gulf War vs nondeployed veterans. Using the Phase II sample, comparing 289 offspring of male GWV, 100 of female GWV, 261 of male non-deployed veterans, and 123 of female non-deployed veterans revealed no significant differences in rates of birth defects in children of Gulf War vs nondeployed veterans.

Discussion:
Dr. Haley inquired how PTSD was determined, asking if a structured interview was used. He stated that structured interviews (such as those using SCIDS and CAPS, two validated approaches for performing standardized interviews to procure information permitting solid psychiatric diagnoses) represent the gold standard, while use of simple questionnaires may lead to spurious diagnoses of PTSD.

Dr. Pellier stated that if soldiers have an unexplained illness, naturally one would expect that they would suffer from stress. A doctor may tell them that either he doesn't know what it is that is affecting them, or that he knows and can't do anything about it: in either case, this can have psychological effects.

Mr. Graves noted that psychiatric responses occur to physical stimuli, such as pyridostigmine bromide and sarin. He emphasized individual variation in response to specific stimuli.

6.

New Research Update
Presenter: Beatrice Golomb, MD, PhD

See **Appendix E** for PowerPoint presentation.

Dr. Golomb presented results of recent, or recently identified findings of relevance to the interests of the Committee. She noted that this research update focused on research related to AChE inhibitors. Some studies pertaining to the character of illness in Gulf War veterans were also included.

The findings were organized into four categories: A. Physiological effects of AChE inhibitors; B. Findings in Gulf War veterans; C. Findings in pesticide (AChE inhibitor exposed) persons; and D. Use of ACh agonists for treatment.

A. Physiological effects of AChE inhibitors
New findings supporting nervous system changes following exposure to AChE inhibitors in animal studies were reviewed. Some of these changes occurred preferentially or selectively in the context of stress, exercise, or heat; while others occurred irrespective of these factors.

Findings included:
- Low levels of DFP (an organophosphate) lead to delayed and persistent brain effects, including protracted reductions in ACh receptors and protracted impairment in working memory. (This impairment was reversed with nicotine treatment.)
- Low levels of sarin lead to delayed and persistent brain effects. Delayed effects, occurring with or without concurrent heat, consisted of reduced M1 receptors, while persistent effects, occurring only in the presence of heat, consisted of increased M3 receptors. Each effect occurred in selected brain regions.
- Low levels of sarin lead to increases in brain mRNA for several cytokines (IL-1beta, TNF-alpha, IL-6); and led to T-cell (immune system) changes.
- Sarin + pyridostigmine bromide (PB) led to changes in cerebral perfusion (significant increases, in the short term; long term follow-up was not conducted), an effect that was amplified when PB was present in addition to sarin.

Studies relevant to interactions and co-exposures included these findings:
1) Even very low levels of pesticide materially enhance later access to the brain of later doses of pesticide (the same class or a different class);
2) Restraint stress plus low level chemicals (PB, DEET, and permethrin) produce that don't occur with either exposure alone, including:
- Region-specific blood brain barrier disruption;
- Neuronal cell death: 30-40% reduction in surviving neurons
- Decreases in M2 receptors in the forebrain, by 20-25%

3) Exercise potentiates effects of low level sarin; and heat potentiates effects of low level sarin. Importantly, sarin reactions were not related to activation of the HPA (hypothalamic-pituitary-adrenal) axis (indeed, cortisone levels of sarin-treated rats were in fact lower than in control animals); and it might be theorized that cortisone, through its anti-inflammatory effects, might reduce BBB permeability induced by inflammatory cytokines. Additionally, brain effects, where they occurred, were brain region specific. Of note, one central effect was inhibited by a peripheral ganglionic blocker, a reminder that central effects can occur in the absence of brain entry of the substance under question, by signaling pathways that in turn have brain effects.

B. Clinical findings related to illness in Gulf War veterans that were reviewed included:
- Gulf War veterans have elevated rates of CFS and PTSD (not new findings)
- CFS patients have altered cholinergic responsivity
- Gulf War veterans have altered cerebral blood flow (ACh inhibitors cause altered cerebral blood flow)
- Muscle symptoms in Gulf War veterans are not associated with abnormal EMG (electromyography) or NCV (nerve conduction velocity) studies (however, they should not necessarily be expected to be).

C. Symptoms in organophosphate (OP) exposed persons.
This was undertaken because those occupationally exposed to OPs represent a group that, like Gulf War veterans, constitutes a previously healthy group with AChE inhibitor exposure.
- A British postal survey found dramatically higher numbers of symptoms among those persons living in an agricultural area who reported OP exposure over the prior 10 years than among those who did not ($p < .0001$). For example, 87% of unexposed persons reported 0 symptoms, vs. 41% of exposed. 41% of exposed reported at least three of the list of symptoms, relative to 4% of unexposed. The symptoms were concordant with those reported by ill Gulf War veterans, including problems with fatigue, cognition, weakness, mood, and smell sensitivity. Symptom patterns were identical whether OP exposure was via sheep dip (diazinon) or other OP exposures.

- A study in greenhouse exposed workers, exposed to low levels of OPs, compared to otherwise similar gardening workers not exposed to OPs, found that the OP exposed group had more fatigue, cognitive/mood problems, irritability, sleep problems, headaches, gastrointestinal dysfunction, and smell sensitivity; as well as reduced performance on some objective neuropsychological tests of cognitive function (such as reaction time). Again, these are all symptoms reported in ill PGW veterans.

- NHIS mortality data show an increase in accidental death in pesticide workers, with an age adjusted RR of 1.6 for men, and 3.2 for women -- both statistically significantly elevated. Selected cancers are also increased.

These findings are critically important because they show that low level AChE inhibitor exposure itself, in previously healthy persons, in the absence of combat, vaccinations, oil fires, depleted uranium, and the panoply of other exposures that occurred in the Gulf,

may contribute to a constellation of symptoms that appears to closely and perhaps precisely mirror that seen in ill PGW veterans, up to and including the finding of increased accidental deaths.

Dr. Golomb reiterated that objective markers were critically important to permit translation between animal and human studies.

She articulated the possible benefits of conducting prospective research on persons entering the pesticide-application field, in whom baseline data could be obtained.

Dr. Golomb mentioned the Bayer experiment in Scotland where volunteers were paid to consume pesticides; and noted that it would be valuable to conduct follow-up study in participants in such studies, ideally prospectively. If future such studies are conducted, baseline testing should be strongly urged.

D. Treatments with ACh agonists
Dr. Golomb reviewed literature showing benefits of nicotine and of nicotine alpha-7 receptor agonists in cytoprotection. Alpha-7 blockers block the protection conferred by these agents.
Nicotine itself has been shown to improve attention and reduce distractibility in humans. Moreover, it was found to normalize persistent deficits seen in mice with prior low level AChE inhibitor exposures (specifically, to repeated low level DFP).
Nicotinic agonists were also found to have pain relieving effects, with distinct receptors involved for nicotine itself, vs. for the agonist epibatidine.
Certain nicotinic agonists were found to improve attention and reduce distractibility selectively in brain damaged animals that had impairments in these functions.
Previously Dr. Golomb had shown benefits of acetylcholine agonists to other domains in which Gulf War veterans report problems, including fatigue, sleep, and gastrointestinal problems. The protection of cells from ongoing injury, found to occur with administration of such agents in animals, had not been previously presented to this group.

7.

Research at Washington, D.C. War-Related Illness and Injury Study Center (WRIISC)
Presenter: Dr. Han Kang, Director of WRIISC, Washington, D.C.

(See **Appendix F** for the presentation.)

Clinical & Research Activities of the War-Related Illness and Injury Study Center
Dr. Kang gave a presentation about the WRIISC. It came into being in accordance with Public Law 1 05-368, The Veterans Program Enhancement Act of 1998, Section 103. The NAS/IOM Committee on a National Center on War-Related Illnesses and Post-Deployment Health Issues came into being in November, 1999. Dr. Kang noted that the VA is actively extending its coverage to include illnesses that may have a causal link to military service and/or deployment.

On August 24th, 2000, the VA released a RFP for the new centers. By May of 2001 two sites had been selected to host these new WRIISC centers; these are located in the Washington, D.C. VAMC and the East Orange, New Jersey VAMC.

The Mission statement of the WRIISC was: "To improve the health of combat veterans through clinical care, risk communication, education, and research, addressing deployment related exposures and the risk of latent illness, injury and disability."

Dr. Kang described the chain of command of the WRIISC-DC Organization.
He described the conceptual model of WRIISC, including, consistent with the mission, components of clinical care, risk communication, research and education and outreach.

WRIISC centers collaborate with the Walter Reed Medical Center and the Center for Health Promotion and Preventive Medicine; and collaborate with universities, including George Washington, Johns Hopkins, and the Uniformed Services University of the Health Sciences.

The core funding of the D.C. program for this year is $1.1 million dollars, to include 8 FTEs (full-time equivalent funded positions). Funding will be reviewed after three years of operation.

The Objectives of Clinical Care were stated to include:
-Develop innovative clinical strategies for war-related illnesses
-Develop effective education techniques for the clinical setting
-Implement clinical algorithms into primary care settings for evaluation of veterans with war-related illnesses

The program unit provides a referral site for veterans who have war-related health concerns and difficult to diagnose war-related illnesses and injuries. This unit serves to examine, manage and provide consultation services to these veterans. There are two major clinical care programs: the WRIISC National Referral Program, and the WRIISC Outpatient Clinic.

National Referral Program
The National Referral program pays special attention to those veterans who might have difficult to diagnose medical problems and who live outside driving distance to the Washington, D.C. (or presumably, New Jersey) facility. In addition, the program serves as a focused second opinion evaluation site for veterans with war-related concerns.

The WRIISC facilities are located in New Jersey (VISN 1-4) and Washington, D.C. (VISN 5-8). However, they serve as a referral site for the remaining VISNs throughout the U.S.

WRIISC Outpatient Clinics
The clinics serve as specialty referral sites, with initial evaluations occurring within the VAMC or at one of the collaborating clinics, depending on what is determined to best

serve the patient's needs. These clinics help coordinate specialty referrals. Ultimately the veteran is referred back to his/her primary care provider for follow-up care.

The Clinical Program interfaces with the National Rehabilitation Hospital, the social work service, DHCC, medical services specialties, primary care clinics, outpatient specialty referrals, and the National Referral Program. Clinical resources include the following:

-EEG/EMG lab
-Sleep Lab and EEG Monitoring Beds
-Neuropsychology Lab
-Magnetic Stimulation Lab
-Multidisciplinary Pain Treatment Program
-MRI
-NRH Specialty Clinic
-WRAMC Deployment Health Clinical Center
-Specialty Consultation Services

The Clinical Status Report showed that the weekly outpatient clinic initiated in April of 2002 evaluated 80 veterans. The inpatient WRIISC referral program figure in January of 2002 had completed 16 evaluations.

Eligibility Criteria:
A new patient must first contact the VAMC eligibility office to be assigned a primary care provider who may then refer the veteran to the WRIISC Clinic. Patients must: qualify as a 'combat service veteran' as defined by DoD, have unexplained symptoms thought to be associated with combat service or other deployment-related experience, be medically and psychiatrically stable for travel, and be willing to participate in evaluation and treatment recommendations.

Research Program Objective
To investigate the health consequences of deployment in a combat theater with a specific focus on deployment-related exposures and the risk of illness, injury, and disability.

Research Interests:

Health consequences of war
Post-service cause-specific mortality from diseases and injuries
New or unusual infections
Chronic medical and psychological conditions
Adverse reproductive health outcomes
Disability resulting from deployment illness or injury
Health care utilization

Dr. Kang showed a chart with 4 major study areas and the respective projects within each.

- Gulf N=700,000; Controls N=750,000
VA/DoD MVA study

- Health Registry: N=70,000; CCEP: N= 30,000
  - Combined VA/DoD Registry Analysis
  - IOM/VA Pre-Deployment Health Study
- Population Based Health Survey: N=30,000
  - Phase I and II Mail Survey, Medical Records Review N=21,000
    - IOM/VA Nerve Gas Exposure Study
    - GW/VA Gulf War Syndrome Clinical Study
    - Neuropsychologic Assessment Study
    - Phase IV Clinical Study: N=2,000; CSP #458, 16 VAMCs
    - 20 Year Longitudinal Health Study
- Health Care Utilization inpatient/outpatient
  - State Tumor Registry D.C., VA, MD, NJ

Research Results:

Mortality Findings

The overall mortality rate of GWV was not higher than non-GWV. However, deaths from motor vehicle accidents (MVA) were significantly higher among GWV. Rates for disease related cases were found to be lower among GWV than non-Gulf veterans. After 5 years the differences in mortality patterns began to dissipate. Mortality rates from both Gulf and non-Gulf veterans remained less than half the rates expected from the civilian population.

Results from the United States and the United Kingdom were remarkably similar.

Health Care Utilization Findings

Dr. Kang cited results indicating that there were not any excessive postwar hospitalizations for the years 1991-1994 due to major categories of diseases in the VA, DoD or California hospital systems. Findings from studies showed, however, that there were significantly more hospitalizations due to mental disorders, diseases of the respiratory and digestive systems, diseases of the skin, and "signs, symptoms, and difficult to diagnose conditions".

National Health Survey Findings: Phase I and II

Physical Health: GWV had reported a higher prevalence of a wide variety of symptoms. They had more serious chronic health conditions, had a lower self-perception of general health, and reported more functional impairment. Health care utilization was greater in GWV than non-GWV.

Psychological Health: GWV self-reported higher incidences of symptoms of PTSD and Chronic Fatigue Syndrome (CFS) (CDC, 1994). The prevalence of PTSD increased monotonically across 6 levels of deployment-related stress intensity (test of trend, $p<0.01$). GWV also reported a higher rate of sexual trauma incidents, e.g.

harassment/assault, while in-theater, which was later associated with the higher prevalence of PTSD after adjusting for combat trauma.

Reproductive Health:
GWV reported a higher incidence of:

- Miscarriages
  - -Male Veterans: OR=1.62; 95% CI=1.32-1.99
  - -Female Veterans: OR=1.35; 95% CI=0.97-1.89

- -Birth Defects (liveborn infants)
  - -Male Veterans: OR=1.78; 95% CI=1.19-2.66
  - -Female Veterans: OR=2.80; 95% CI=1.26-6.25

Symptom Cluster:
A cluster of symptoms consistent with neurological impairment included the following symptoms:

- -Blurred vision
- -Loss of balance/dizziness
- -Tremors/shaking
- -Speech difficulty

The symptom complex appeared to correlate with objective neurological abnormalities including abnormal ENG (electronystagmography). GWV reporting symptoms were found to have been in military duties in Kuwait and Iraq, and the symptoms complex was associated with exposure in the Khamisiyah nerve gas plume incident, following the munitions depot demolition at Khamisiyah. (Details on this finding have been published: Kang HK et al 2002, Arch Environ Health 57: 61-8).

Current Studies:
Dr. Kang then reported on the current studies in which the VA is involved. These include:

- Fatal Motor Vehicle Crashes of GWV and non-deployed veterans
- Mortality and Morbidity among US GWV who were potentially exposed to nerve gas at Khamisiyah
- Study of Health Outcomes and Environmental Surveillance (SHOES) in Bosnia/Kosovo
  - -Collaborators:
    - Army Medical Surveillance Activity
    - Deployment Environmental Surveillance Program

Aims of SHOES:

- Develop a model data repository linking military service records and VA records
- Combine advances in exposure assessment with health and illness data to investigate the effects of deployment of armed forces personnel on health
- Explore topical research questions and validate findings of other veteran cohorts

Specific Applications of (SHOES)

-Is there an excess mortality from MVA among Bosnia/Kosovo veterans as with other veteran cohorts?
-How were environmental exposures correlated with short and long-term health outcomes?
-How do environmental monitoring data correlate with biomarker data?

Longitudinal Health Study of Gulf War Era Veterans
PIs: Han Kang, DrPH; Seth Eisen, M.D., St. Louis VAMC; Charles Engle Jr., M.D., WRAMC
Study Design:
-Longitudinal study of a permanent panel of 15,000 GWV and an equal number of non-GWV identified for the National Health Survey
Aims:
-Determine the health status of GWV relative to non-GWV ten or more years after the war
-Characterize how the health status of GWV and non-GWV has changed in the past 5 years.
-Compare the current health of GWV with civilian peers.
-Assess the role of complementary and alternative medicine in the health of GWV.

Dr. Kang kindly permitted the RAC-GWVI to insert two questions into a survey questionnaire already approved by OMB to allow veterans to be asked what treatments have they tried and what were the results.

Discussion

Dr. Steele thanked Dr. Kang for his interest and assistance in enabling the treatment questions to be inserted in the study.

Mr. Robinson asked why both centers were on the East Coast.

Dr. Kang replied that there were no proposals from the West Coast and if there are patients that cannot get to the East on their own, then the government will fly them to the clinic.

Dr. Haley asked what the capacity of each clinic was.

Dr. Browne, from the audience, replied that the capacity is one patient per week per facility.

Additional comments by Dr. Kang:
We specifically looked for PTSD and CFS and also higher rates of sexual trauma within the sample population. We found potential concerns related to problems with reproductive health and clusters of factors such as dizziness and speech difficulty among GWV. There were higher rates of illness among those under the Khamisiyah plume based

on the 2002 model, and higher rates in those who were in combat and in Kuwait and Iraq during Desert Shield and Storm. There were more motor vehicle accidents among GWV. We are looking at the health of troops in Bosnia and Kosovo and have identified 50,000-60,000 veterans. We would like to have a single database to permit all the data to be put in one place.

We are also involved in the Millennium study following troops spanning the entirety of their careers. The Millennium study is a cross sectional study started in 2000. To be part of the study, a soldier must be on the rolls. The core study is based 100,000 soldiers on active duty since 1997, deployed since then in SE Asia, Kosovo, or Bosnia. The study is exclusively a stratified, random sample of servicepersons.

8.

Research at the New Jersey WRIISC
Presenter: Dr. Tom Findley, Director of Research, NJ WRIISC

(See **Appendix G** for the original presentation.)

The website for the WRIISC is www.wri.med.va.gov. Dr. Finley encouraged the Committee and members of the audience to visit the website for more information on activities and services provided at the WRIISC in East Orange, New Jersey. He stated that they get about 80 'hits' per day and that they hope that the number will increase very soon. Dr. Findley said that the website, in addition to providing materials and patient friendly summaries of information, also has interviews and chat rooms to give the veteran a sense of personal attention to their needs.

Dr. Findley gave brief descriptions of the individual research areas members of the New Jersey WRIISC staff. Their major job is to generate research proposals in the area of CFS, FM, sleep, cytokines, behavioral illness, the adrenal-pituitary axis, the perception of symptoms, research training and research skills. Dr. Helmer is Associate Director of clinical projects. Dr. Santos, Associate Director of Risk Communication, works with risk perceptions. Dr. Cook is conducting research in the areas of CFS and exercise. Dr. Servatius is working on physiology, the CNS effect of PB and stress. Dr. Weaver also is working on the effect of stress and toxins, neuronal protein markers and the adrenal axis, the role of butyrylcholinesterase (BuChE) and paraoxonase (PON). Their work is funded, in addition to the VA and DoD, by the NIH.

Consultation Services

Dr. Findley explained that they provide consultation services and evaluate medical records for missed diagnoses or inadequately treated conditions. He said they personally evaluate the veteran for new diagnoses and fully discuss all deployment–related health concerns with patients. They perform the necessary tests to confirm or deny diagnoses, within their capabilities, and make recommendations for treatment and/or home care follow-up care.

Involved in a standardized consultation are the following features:

History and physical

Psychological assessment
Risk communication interview
Fitness testing
Sensory testing
Balance testing
Education session

Educational Goals of the New Jersey WRIISC Center

Provide education and educational resources
Support Clinical Program and Risk Communication activities
Conduct educational research to improve access or use of education and resources

Education Activities

Articles are prepared for features in veteran's magazines, and fact sheets are distributed to VSOs. The fact sheets explain medically unexplained illnesses, the benefits of exercise for patients, and other relevant information. Project proposals are submitted for testing delivery methods of health education to soldiers being deployed at Fort Dix, New Jersey. Monthly seminar series for health care professionals are also held in an effort to keep researchers abreast of up-to-date research.

Risk Communication Activities

The division of Risk Communication helps provide continued support to the Clinical Programs in their performance of initial and exit interviews and in preparation of patient friendly summaries.
It also prepares material for the website and prepares presentations on Risk Communication and Unexplained Illness for medical Grand Rounds.

Activities have included development of instruments to explore how veterans think about deployment related exposures (risk of exposure, symptoms vs. disease, health care management, etc.) and to explore veteran's perception of stress and its relationship to health outcomes.

Research Activities

Areas covered in this section include: physiology of unexplained illness, health services and systems, perception of symptoms, and research training. Two pilot studies have been funded by WRIISC.

Grants Funded/Pending:
-Physiology of Unexplained Illness (29)
    -Stress(5), Pain (3), Sleep (4), Balance (2)
    -Neurophysiology (9), FM/CFS (6)
-Health Services and Systems
    -LVHS large data base (8), Providers (2)
    -Utilization (3)
-Perception of Symptoms (12)
    -Symptoms (8), Risk communication (4)
-Research training (4)

Research Interests and Projects at New Jersey WRIISC

Researcher	Expertise/Interest	Funded	Pending
Benjamin H. Natelson, MD, Director WRIISC, New Jersey	Medically Unexplained Symptoms (MUS), Behavioral Medicine, Adrenal Axis	NIH CFS CRC, VA MR -Physiology and natural history of CFS -Adrenal function in GWV with CFS	NIH RO1s: Sleep and Cytokines in CFS and FM; VA HSRD: VA Communications about Bioterrorist Attacks
Thomas W. Findley, MD, PhD	Phsyciatry; disability, functional assessment; mathematical modeling	HSRD IIR	HSRD REAP Pilots: Balance Deficits; Health Services Rehab. Research Center (LOI) VA Rehab: Mathematical Modeling of balalance To evaluate interventions (LOI)
Susan L. Santos, MS, PhD	Risk communication and Risk Perception of Deployment Related Health Risks, differences in perceptions of VA physicians/veterans about medically unexplained illness, communicating risks and benefits of preventative measures, environmental risk communication	NEIHS grant (with Boston Univ.)	Pilot: Risk perception of veterans with MUS -VA HSRD Bioterrorism: DoD deployment related message dev.; US EPA NCER: comparative use of 3 evaluation tools to empower communities in the cleanup of sediment contaminated sites
Liesel Copeland, PhD	Educational and Survey Research, web based education and program evaluation	VA VISN: templates for drug ordering and evaluation of their utility	DoD: Evaluation of different methods for predeployment education. Risk communication about stress and MUS.
Drew Helmer, MD	Internal Medicine, ambulatory care		VA HSRD: bioterrorism and communication in

	utilization, risk communication		the VA, preventable hospitalization in diabetes Planned: VA HSRD: Health care utilization in vets with MUS and those with diabetes
John Ottenweller, PhD	Long-term effects of chronic stress, adrenal axis, BuChE, and PON	VA MR, WRIISC Pilot: CNS mechanisms governing persistent stress effects, Cortisol, BuChE and PON in Gulf Era Veterans	VA epidemiology: cytokines in Gulf Era Veterans and Spouses
Dane B. Cook, PhD	Exercise physiology, psychophysics, pain and fMRI	WRIISC Pilot- measuring pain sensitivity, exercise-induced analgesia and cytokines in Gulf Vets with pain	VA MREP: functional brain imaging (fMRI) of pain in GWV who have unexplained pain
Richard J. Servatius,PhD	Physiological psychology, Learning and Behavior, Stress and PB	VA MR, NIH -CNS effects of combining PB and stress -Learning and Memory in CFS	
Shelley Weaver, PhD	Adrenal axis and individual differences in responses to stress and toxins		VISN 3 SEED and NIH RO3 Pilots: Neuronal protein markers of persistent effects of severe stressors -proteomic analysis of cerebrospinal fluid in patients with medically unexplained fatigue
Karen Quigley, PhD	Physiological and psychological factors in stress reactivity	CFS CRC Pilot; ONR -balance testing in CFS -Cognitive modeling of stress reactivity	VA MRS, VA HSRD -Risk communication, stress and experimental vaccines -Prospective study of stress reactivity and psychosocial factors pre-deployment affect post-

			deployment health

Roles of BuChE, PON and Stress in MUS (medically unexplained symptoms)
Dr. Alpern was assigned as project statistician. Assay data from 3,257 samples was sent to Hines Co-operative Studies Center with expected preliminary analyses by February of 2003.

Pain Sensitivity in Gulf War veterans with Unexplained Musculoskeletal Pain.
A psychophysiological assessment procedure has been tested and found to be reliable. A luminex cytokine analyzer was calibrated and tested. To date, five subjects (3 healthy and 2 ill) have been tested with an additional 10 subjects scheduled. The preliminary evidence has shown heightened pain sensitivity in Gulf War veterans with unexplained pain.

Postural Stability: Mathematical Modeling
Mathematical modeling is underway with one model applied to existing data, and another under development. Such models have been useful in past settings. For instance, when an astronaut has a cold, NASA has found that such modeling is effective in assessing how long it will be before before he or she can go up in space again.

Ankle stiffness from the balance test has been calculated with testing on 17 veterans, 10 CFS subjects and 8 controls. The CFS subjects and veterans had a decrease in balance. Dr. Findley stated that if balance is off, persons will be afraid of falling and will tense muscles, which will cause fatigue. Future plans call for adding position sensors for additional elements to include in the model. A scientific paper has been submitted on this research. [Dr. Golomb comment: if balance is off, irrespective of "fear" of falling, there will be greater usage of muscles during the righting response, to compensate as imbalance begins to induce deviations from stable upright posture.]

Prospective Study of Functional Status in Veterans at Risk for MUS
Quigley, Findley, Helmer, Weaver, et al.

Aims of the Study (briefly stated) :
Aim I: To determine whether pre-deployment variables, such as personality traits, and behavioral and physiological tendencies, are associated with poorer post-deployment functional status.

Aim II: To determine whether pre-deployment coping style and pre-deployment social support, as well as immediate post-deployment social support, help in buffering reduction in post-deployment functional status.

Aim III: To determine whether immediate post-deployment variables, such as decreased functional status, decreased emotional control, increased psychological distress, and increased/decreased social support are predictors of later increased health care utilization.

Discussion:

Dr. Golomb asked if there were a mechanism to permit the serviceperson to answer the predeployment and postdeployment questions without concern that honest disclosure of health problems or concerns may jeopardize the person's military career. Dr. Findley answered that only the researchers are allowed to see the data.

Dr. Haley asked Dr. Findley is they have had a chance to postulate from where these MUS issues were coming, and particularly if they have considered the brainstem.

9.

EN101 Antisense Drug
Presenter: Dr. Hermona Soreq, the Hebrew University of Jerusalem

(See **Appendix H** for the paper that formed the basis of the presentation.)

Dr. Soreq presented a synopsis of her work on the retrieval of cholinergic balance by antisense oligonucleotides, spanning the range from animal models to clinical trials. She explained how scientific evidence has demonstrated alternative splicing patterns of gene products controlling numerous physiological functions.

The AChE enzyme is involved in cholinergic neurotransmission. Under certain conditions, including stress and AChEi exposure, overproduction of a rare read-through variant, AChE-R mRNA, is induced. The effect, once induced, persists indefinitely (evidently for the life of the animal). In mice, this overproduction is associated with electrophysiological hyperactivity, impaired working memory, hypersensitivity to head injury, prolonged contextual fear responses and weakened muscles. These symptoms are temporarily alleviated by murine (m) EN101, an antisense oligonucleotide that selects for and induces the destruction of mouse AChE-R mRNA.

Myasthenia gravis patients are exposed to AChEi as therapy for their problem, and thus are subject to development of this gene product. (Dr. Soreq stressed that presence of this product may have a useful physiological function in the initial contexts in which it is induced; however, the change persists long after the utility has passed.) In a human clinical trial, myasthenia gravis patient volunteers responded to one week of oral hEN101 administration with marked improvement in muscle function. Dr. Soreq demonstrated such dramatic improvement in a patient with myasthenia gravis, showing video clips comparing performance on tasks including speed of drinking a glass of water (normally a very difficult task for untreated myasthenics); and duration of ability to hold up the head while recumbent. Comparing the new treatment to established therapies, the speed at which a glass of water could be swallowed was dramatically improved, and the duration for which the subject could continue to elevate the head, while supine, was markedly extended.

Discussion:
Several Committee members thanked Dr. Soreq for remarkable work, and an excellent and highly understandable presentation.

The committee agreed that an important next step would be to assess for the variant AChE-R in ill Gulf War veterans. If ill Gulf War veterans are found to more commonly have the AChE-R, there would be significant reason to recommend testing her anti-sense therapy in ill veterans.

10.

Treatment Research Concepts
Presenter: Dr. Lea Steele

(See **Appendix I** for the PowerPoint presentation.)

Dr. Steele presented draft recommendations drawn from work products of the Committee during the last year. Recommendations fell into three categories:

I. A recommendations that the VA establish a program specifically tasked with proactively identifying, developing, and evaluating treatments for GWI.

II. Two appendices outlined considerations for prioritizing treatments for study; and identifying treatments being used and assessing evidence for effectiveness.

III. An additional section/ appendix to possibly recommend studies of specific treatments.

If the Committee agrees that the VA should establish a program as outlined in part I, then the two appendices in part II further the process of prioritizing study recommendations and identify putative treatments. Part III entails recommending specific treatment trials to the VA.

Federal imperative

Dr. Steele reviewed background materials from the U.S. Congress, the Federal PGW Coordinating Board, and the VA that have designated identification of treatments for GWI as a top priority issue. The VA has maintained open solicitations for GWI treatment trials since 1997; however few treatments have been studied. The major exceptions have been the joint DoD/VA antibiotic treatment trial in mycoplasma-positive veterans; and the exercise and cognitive-behavioral therapy trial, which Dr. Nelda Wray reported on earlier in the program.

The IOM and the Hierarchy of Evidence

The Institute of Medicine (IOM) panel recommended using a 'hierarchy of evidence' approach to undertaking treatment research, Dr. Steele reported. However, she noted that virtually no progress has been achieved in undertaking such a research program.

Research is investigator initiated

Dr. Steele said that most research is investigator initiated; scientists like to study what is of interest to them. At the VA, it is no different. There is no mechanism for proactively identifying treatments or developing evidence in support of candidate treatments for trials. There is not a system of evaluation of outcomes associated with treatments used or

recommended for unexplained illnesses in Gulf War veterans. She said that it is highly unlikely that there will be any success in finding treatments without a new approach.

Success not likely without a new approach

Dr. Steele said that the current approach has not produced any results. GWI is a difficult area to study, and the condition is likely to be difficult to treat. There is a need for sufficient interest in the area, as well as expertise in treating these unexplained illnesses among the VA clinicians who are seeing ill Gulf War veterans and their family members.

Recommendation

Dr. Steele proposed the following for consideration by the Committee:

I Establish a comprehensive program to proactively identify, develop, and evaluate treatments for GWI

- Staffed by professionals with appropriate expertise
- This program would be in addition to existing VA research programs
- Additional new initiatives would provide a framework for evidence based identification and development of treatments

She said that the new program initiative would include:

- Identifying treatments currently being used
- Determining outcomes associated with current VA recommended treatments
- Generating a plan for developing and testing untried treatments
- Generating a program protocol for assessing evidence related to treatments, and determining the next step in the process
- Technical assistance to clinicians for developing data re: treatment effectiveness
- Establishing guidelines and standards for GWI treatment research

II Two Appendices:

a) Considerations for Prioritizing Candidate Treatments for Trials (previously circulated by Dr. Golomb)

1. Evidence of effectiveness
2. Safety
3. Range of symptoms expected to benefit the patient from treatment
4. Strength of biological rationale
5. Difficulty and cost of evaluation
6. Current usage of treatment by veterans

b) Considerations for Identifying and Evaluating Treatments That Have Been Used to Treat Unexplained Illness

1. Identify treatments currently being used within and outside the VA
   a) Existing VA clinical records
   b) Survey veterans and clinicians
2. Assess effectiveness of treatments currently being used
   a) By review of existing clinical records
   b) By follow-up with veterans treated at PGW clinics
   c) By establishing outcomes monitoring programs

d) By learning of the experience of other agencies in developing protocols for evaluating unstudied treatments in clinical practice

3. Develop additional data when indicated

a) By evaluating evidence re: treatment, to determine the appropriate next step

b) By providing technical assistance for clinicians to collect interpretable data

c) By establishing a review panel to prioritize and advise on the next steps to be taken

Experience of Other Agencies re: Evaluation of Unstudied Treatments in Clinical Practice

Usual drug development model depends on extensive preclinical data

-This is not currently available for GWI

-1990: OTA proposed a mechanism to evaluate novel cancer therapies in medical practices to identify preliminary evidence of disease improvement

-National Cancer Institute: "Best Case Series" program for evaluating novel cancer therapies

-NCCAM: "Prospective Outcomes Evaluation and Monitoring"

-CDC: Adaptation of epidemiology field methods to clinical practice evaluation

Lessons Learned

- Requires clear documentation of disease, treatment, and health outcome
- Routine clinical data is often not adequately informative
- Technical assistance needed for clinicians
- Outside review panel useful in prioritizing treatments for study, recommending next steps

Suggested RAC-GWVI Recommendations:

1. Recommend that the VA establish a comprehensive program to proactively identify, develop, and evaluate treatments for GWI.
2. Recommend adoption of the suggested Considerations for Prioritizing Candidate Treatments for Trials: Appendix (a).
3. Recommend adoption of Considerations for Identifying and Evaluating Treatments That Have Been Used to Treat Unexplained Illness: Appendix (b).
4. Uncertain: Should RAC-GWVI Recommend that the VA study specific treatments that have not yet been tested in ill veterans?

Preliminary List (as previously discussed by Committee)

Treatments targeting ACh system to counter ACh dysregulation

Israeli antisense drug to target AChE-R (alternatively spliced, water soluble AChE)

Other -- e.g. nicotinic or muscarinic agonists

Treatments that may benefit mitochondrial function, and thus cellular respiration

a. CoQ10

b. Other

Treatments that may enhance blood or oxygen delivery
e.g. Hyperbaric oxygen, Ginkgo biloba, erythropoietin, salt
Other
Other treatments used in CFS, MCS, FMS
a. Sauna detoxification therapy
b. Other

Pros:

Good hypotheses, should be pursued
Unlikely that these treatments will be studied without specific recommendations
Would serve as examples of general approaches worth considering
Convey to veterans, VA, researchers that Committee has reviewed and considered specific treatments

Cons:

Some associated with no clinical experience for GWI or similar conditions
In some cases, rationale for use also speculative
Can a government agency administer a therapy for which there is no preliminary indication of effectiveness? Should they? [BG comment: No. The strength of rationale is obviously important. For none of the domains discussed is there a complete absence of indication of effectiveness, but for any proposed treatment, this would need to be developed by the investigator; or if RFAs were generated for research contracts, by the contracting agency.]

Discussion:

Mr. Binns said that the Committee should be reporting on what it has learned regarding treatments and as to what they think is the appropriate action for a particular treatment candidate. For example, on a particular treatment, the Committee may take the position that it needs some more investigation before it can be determined if it should be investigated in full clinical trials or not. It will allow us to be constructive without advocating testing of a particular treatment for which limited evidence is available. He said that this topic would be considered at tomorrow's session.

11.

Presentation on VA Actions to Publicize New Initiatives
Presenter: Mr. Jeffrey Phillips, DAS Public Affairs

Mr. Phillips reported on plans by the VA to disseminate research findings and opportunities for new research, and plans to get the media to attend to these issues. He observed that they needed to find a way to 're-legitimize' the research. While such research has always been important and legitimate, it has not always been viewed in that light. He commented that the VA has been disappointed with the media, and remain disappointed in the lack of coverage they are receiving. Relatively little attention has been paid to the fact that the DVA has set aside $20,000,000 for deployment related health, including research toward finding treatments for GWI.

He stated that their plan included forming a relationship with trade journals, reporters and with specialty sites like Rx.com and Lexus Nexus. He said plans include working with Dr. Wray and her staff, and working through internal channels within the VA. He told the Committee members that he hoped to have a US Medicine person write an article on the VA research efforts to date.

Mr. Phillips said that he thought that they should outsource, and that he would be looking at military.com, seeking to use their email list to reach veterans. He noted he would ultimately like to reach an audience of six figures.

Discussion:
Dr. Haley asked Mr. Phillips what the Committee can do to help him. He replied that every Committee member should get out in his or her community and talk about the VA research opportunities.

Dr. Steele wanted to know how the VA would undertake educating their own doctors about the announcement of the $20,000,000, and inquired whether they had concrete plans directed to that end.

Mr. Phillips said that maybe some members of the Committee could drop by his office and talk about their ideas with him.

Dr. Steele said that she knows that Dr. Kang sends people out to do Grand Rounds to tell them what is going on with their work.

Dr. Golomb volunteered that at the VA in San Diego, VA videos are sometimes shown during biweekly faculty meetings for the FIRM clinic (outpatient clinic) physicians. Videos, such as those of Secretary Principi giving a statement, are not uncommon. Similar videos could be generated for use in that, and related venues. There was some agreement that this was a good idea.

Dr. Steele stated that, in Kansas, she had been in a video related to GWI, that such videos could be used to get the message out to the community.

Mr. Phillips concluded his presentation by giving the Committee his email address and inviting any and all suggestions to be brought to his personal attention. The email address is: Jeff.Phillips@mail.va.com

12.

PUBLIC SESSION:

*** Dr. Meryl Nass** said that one of the PI's had told her that the ABT trial had failed because patients became non-compliant and discontinued taking their medications and therefore, the study became non-significant. She said that oil well fires seemed to have been excluded as exposures and putative causes, and that they too can cause psychiatric problems. She also said that she has tried to push for autopsy data from all major VA

centers regarding all kinds of diseases and that that information has not been forthcoming. She mentioned the data from one anthrax vaccine patient who died post September 11th due to an autoimmune disease, but that the information was not disclosed.

Sixty per-cent of Dr. Nass's practice consists of ill GWV, and she said she would like to share some of the treatment options she has used with them. She said it is important not to just try one thing or to just give one treatment at a time. She noted that each veteran is different, and needs individual treatment protocols, and that the physicians should look at them as individuals who are ill. She said she said she can never tell how well they will respond when they walk into her office. All of her FM patients improve. Her GWV rate of improvement is about 50%. Dr. Nass said that the longer they have been ill the harder it is to help them.

Dr. Nass shared her list of treatment options with the Committee and public.

*** Ms. Denise Nichols**: We have to think about another group of ill soldiers coming to the VA doorsteps, and they will; what are we going to be able to tell them? What hope are we going to be able to give them? We have to look to the future. We wanted lessons learned and those lessons were to have included small scale studies like those done by Dr. William Rae; hyperbaric Oxygen, CoQ10. We were supposed to know by now where soldiers were in the theater, and to what they were exposed. They aren't even coding them, from what we heard today. Just look at the last two GWVIS reports and see how many of us are dying; 538 conflict deaths; 179 deaths per month. I don't know about the British deaths or the others who fought or who were with us over there. What are the normal death rates? We need to know this information. We need to know and have been asking these same questions over and over again. Where were we located. Give us the data, and let's find out how they died. Doesn't the country owe us that much? Thank you very much for your time.

*** Mrs. Alison Johnson** had a question about how birth defects were measured and about the concept of 'intact marriages'. She said that she didn't think that the criterion was adequate because a person could have just been married and wouldn't have had the marriage during the Gulf War. Since many marriages did not survive, a mechanism is needed to collect the data from the families of the era. She said that we would need to include all spouses from 1990 to the present and do some sort of sorting to get more accurate data.

Ms. Johnson described a clinic in Santa Fe, New Mexico that treats MCS patients using infrared sauna as a treatment modality. She reported information from the clinic saying that patients could tolerate the sauna for a longer period of time. She told of a case of a woman who was sprayed with pesticide on her face who went through the infrared sauna treatment and who now is almost well. Ms. Johnson said that the cost of the units is about $3,000 and that the patients needs to drink a lot of water and take minerals after the exposure.

She conveyed others' opinions about hyperbaric oxygen, the need for testing, and possible theories about mechanism.

*** Dr. Meryl Nass**, from the audience said that she has heard that hyperbaric oxygen can loosen dental fillings and wanted to know if there are more scientific studies available.

February 4th, 2003
Room 239

13.

Research Recommendations; Ideas for Discussion
Presenter: Dr. Beatrice Golomb

(See **Appendix J** for the original presentation.)

Dr. Golomb discussed an outline of research recommendations that represented the synthesis of discussions with the Expert Panelists; and teleconferences between August of 2002 and January of 2003 with a group of leading neuroscientist who are experts in the field of acetylcholine and acetylcholinesterase inhibitors; and respected clinical neurologists.

Draft Research Recommendations: Focus on AChEi
The following general recommendations were endorsed with strong and essentially universal agreement:
-Genetic & Pharmacological Animal Models
-Objective Markers
-Studies of Other AChE Exposed Groups
The following additional recommendations were endorsed with strong but not universal agreement:
-Treatment Trials
-Brain Banks
-Genomic and Proteomic Screens

Genetic & Pharamacological Animal Models
Advantages
-Help to define mechanisms
-Help to identify objective markers
-Provide means for developing treatments
-Provide means for translating treatments from animals to humans
-Provide means for monitoring treatments
-Already leading to critical insights and promising ideas re: treatments.
As one of the members of the Expert Panel said, "What's not to like"

Objective Markers
Identify objective markers that result following AChEi exposure, pertaining to

1) Changes in ACh system function

2) Altered biology distinct from ACh system function (e.g. membrane effects, oxidative injury, cytokine changes, mitochondrial effects)

Identify objective markers irrespective of AChEi, markers associated with illness in Gulf War veterans (e.g., squalene antibodies)

Advantages:

-Help to define causes: Identify in animals which exposures and exposure combinations produce the relevant objective marker

-Define illness subsets: Subsets of ill veterans may have different illness cause, natural history, and response to treatment. Pattern of objective markers may distinguish such groups (can use techniques like unsupervised neural networks to identify clusters.)

-Permit translation between animal & human studies

-Define targets for treatment

-Permit targeted study of disease (natural history, prognosis)

-Treatment trials can be targeted to those in whom benefit might be seen (enhance power, reduce cost, reduce morbidity)

-Once demonstrated to be successful with trials, tested treatments can be targeted to those who may benefit (reduce cost, reduce morbidity)

Study Others with AChEi Exposure

Capitalize on natural and experimental exposures to AChEi (OPs and Carbamates), emphasizing previously healthy populations. Some evidence already suggests they have similar health problems, and similar genetic and biochemical risk factors.

Advantages:

- Can retrospectively assess for health problems (exposed-unexposed)
- Can prospectively assess for health problems (e.g. people entering pesticide field vs. unexposed control) to define which PGW outcomes pertain. This cannot be done in tests of Gulf War veterans themselves, but provides information critically relevant to that group.
- Can define susceptibilities (PON levels) without effect/cause contamination.

-Can test PGW markers to define if marker is linked to AChEi exposure (or ill subset among AChEi exposed) in humans. (Provides a group without the full complex of alternative exposures—vaccines, DU, combat stress).

-Can follow populations with known dose exposure (e.g. Bayer trial in Scotland) vs. controls.

Caution: some such populations may have had single exposure. Effects may depend on repeated or persistent exposure.

-If the AChEi hypothesis is supported, the implications directly extend to civilians and the current military population, who are at risk of chemical weapons (AChEi) attack by terrorists or opposing military forces. Thus, this research has critical significance beyond Gulf War veterans, in understanding the effects of chemical weapons and physiological mechanisms which may form the basis for the development of medical countermeasures.

Develop a Brain Bank
Develop a brain bank, possibly contracting with existing banks for tissue preparation and banking.

Advantages:
- Can test selected hypotheses about mechanism – e.g. evaluate presence, in ill veterans, of aterations in absolute number & ratios of specific neuron and glial cell types, receptor binding sites, etc.
- Can enlist veteran advocacy groups for help in collecting material from deceased patients, and from those friends and families who are interested in assessing this effort (who can provide control materials).
- The national VA healthcare system can be capitalized upon to implement uniform tissue collection and preparation procedures.
- Commencing collection now will forestall delays later, as hypotheses 'catch up' and are in need of autopsy samples for testing; otherwise, as hypotheses are developed, if the banking process has not preemptively begun, there will be no tissue with which to conduct hypothesis testing.
- Such brain banking has provided important insights in Alzheimer's disease, Huntington's disease, and other neurodegenerative conditions.
- It would be unfortunate not to capitalize on this vital information, when veterans and others are amenable to donation of brain tissue.

Disadvantages:
- There will be a time lag before sufficient samples are available for meaningful interpretation (though this is mitigated by starting now).
- Hypotheses may not be "there" yet (however, this and the time-lag concern are mutually mitigating)
- Disparities in methods of tissue collection/preparation may affect utility of samples (this is mitigated by developing uniform collection and preparation procedures, and implementing at least throughout the VA healthcare system)
- Costly

Genomic/proteomic screens
Conduct genomic and proteomic screens of ill PGWV vs. controls, using gene and proteomic arrays. Use patterns of results and sophisticated statistical techniques to distinguish ill PGW veterans vs controls. Proteomic screens may be driven by experts/hypotheses.

Advantages:
-May identify factors or factor clusters that distinguish ill PGWV vs. controls (objective markers, even if based on a cluster).
-May identify factors or factor clusters that distinguish different illness subsets, among ill Gulf War veterans. Illness subsets may emerge based on clustering in n-dimensional space
-Has yielded benefits for other unexplained multisystem illness conditions (CFS), to track treatments (proteomics).

Disadvantages
-Cost
-'Shot in the dark'- vs. hypothesis driven (though consultation with experts can render it hypothesis driven).

Treatment Trials
-Support treatment trials for agents currently being used by ill PGW veterans. This is a matter of safety for current veterans.
-Support treatment trials of products that target mechanisms shown to be disrupted by AchE inhibitors (ACh mechanisms; mitochondrial mechanisms; oxidative injury/apoptosis; downstream products of ACh, e.g. neurotransmitters and other body chemicals and functions regulated by ACh).

Advantages:
-May lead to benefits to health in PGW veterans--& others
-May save cost/effort/health by directing veterans away from those treatments that are determined not to be useful, or that are found to be harmful.

Disadvantage:
-Harm of treatments
- Cost of trials
-?Premature?

Brief Review of Sample Treatments:
Cholinergic agonists
A. Nicotinic Agonists:
Choline is a precursor to acetylcholine, and additionally has direct alpha-7 nicotinic AChR binding. It and other alpha-7 agonists offer cytoprotection (protection against cytotoxicity) when cytotoxicity is induced in experimental models. (Jonnala RR et al, Synapse 2003 47(4):262-9).

Nicotine has neuroprotective effects, possibly because it upregulates alpha-7 nicotinc receptors (Terry AV et al 2002. J Pharamacol Exp Ther 2002. 301(1):284-92). Nicotinic pretreatment reduces cell death caused by cytotoxic environment (deprives cells of NGF and serum). However protection is blocked if selective alpha-7 blocker MLA (methylcaconite) is given. Other tested nicotinic agonists are also protective if given although less so than nicotine. The next most protective group among agonists tried included epibatidine, 40HGTS-21, methylcarbamylcholine, and 1,1-dimethyl-4-phenyl-piperazinium iodide. The most protective ones increased labeled alpha-bungarotoxin binding sites the most, again suggesting that upregulation of alpha-7 may be the mechanism.

Nicotine improves attention and reduces distractibility in humans (literature in dementia and normals). Nicotine normalized persistent deficits in memory function in rats

previously exposed to repeated low level DFP (Stone JD et al 2000. Brain Res 882 (1-2): 9-18).

Nicotinic agents administered systemically have pain-relieving effects if there is nerve injury. The alpha-4-beta-2 subtype of nicotinic receptor was responsible with nicotine, while a different receptor was involved when epibatidine was administered. Muscimol, a GABA agonist, also has this effect; and GABA blockers had opposite effect, suggesting the ACh-GABA system is responsible. (Rashid M, & Ueda H 2002, Brain Res 953:53-62). (ACh is involved in presynaptic regulation of GABA.)

SIB-1553A is an agonist of the human beta-4 nicotinic receptor: its administration led to improved attention and reduced distractibility in rats with impairments in the relevant tasks (but not in normal rats). Impairment was produced by the NMDA antagonist dizocilpine (Terry AV et al 2002. J Pharmacol Exp Ther 2002. 301 (1): 284-92).

Muscarinic M-1 Agonists
Talsaclidine improved performance on a memory test in rhesus monkeys by 7-10% (delayed match to sample). WAY 132083 improved performance on a memory test in rhesus monkeys by 16% (delayed match to sample). Different doses were optimal for different animals (Terry AV, et al. 2002. Psychopharmacology (Berl) 162(3): 292-300).

ACh Agents, summary
ACh enhancers: agonists, AChEi, etc have been reported to lead to:

ANIMALS	HUMANS
Improved cognitive function	Improved cognitive function
Pain relief	Pain relief
Fatigue and weakness	Reduced fatigue/increased strength
Protection of cells from ongoing injury	
	Benefit to GI function
	Sleep, under study
	Mood being studied

14.

Antisense Approach to Isoform-Specific Blockade of AChE
Presentation by Dr. Hermona Soreq

Dr. Soreq gave background history about the difficulty of inhibiting certain nervous system enzymes and receptors pharmacologically, because sometimes the target protein is a subtype within a family of closely related gene products; it may be easy to fool the drug looking for its target. Antisense oligonucleotides attack unique nucleotide sequences rather than a three dimensional protein structure. In other words, they look for the linear

sequence of nucleotides rather than the three dimensional structure of the protein, what the protein "looks" like. This, Dr. Soreq said, makes antisense oligonucleotides a powerful tool to discriminate between closely related proteins.

Due to the vast complexity of the mammalian central nervous system, and the variety of neurotransmitters and their receptors, she emphasized how important it would be to find a way for drugs to selectively target an element of this system. An antisense approach to isoform specific blockade of AChE, for example, represents one such mechanism.

Dr. Soreq described some of the ways antisense technology has been able to distinguish between members of the D2 class of dopamine receptors. Antisense autoreceptors in dopaminergic neurons in the substantia nigra part of the brain of treated rats were able to elicit physiologically significant reductions in either D2 or D2 autoreceptors (Tepper et al 1997).

Classification and characterization of the opioid receptors, mu, delta, and kappa has been greatly assisted by antisense technology; Dr. Soreq quoted from research reported by Pasternak and Pan, 2000.

In work that has particular significance to ill Gulf War veterans, Dr. Soreq reported on AChE as the target protein of pesticides and chemical warfare agents (as well as PB). Temporary inactivation of AChE prolongs the half-life of released ACh thereby enhancing postsynaptic signals. She noted that limitations restrict the therapeutic utility of pharmacological AChEi.

Limitations of AChE pharmacology

Specificity:

Structural and functional homology between AChE and BuChE: both are carboxylesterase B serine hydrolases, and they share 52% identical amino acids

	AChE	BuChE
Hydrolyze ACh	Yes, but specific about substrate	Yes, but more permissive
Concentration in plasma		higher
Isoforms	AChE-S unique 40 amino acid C terminal peptide encoded by exon 6	
	AChE-E erythrocyte bound form encoded by mRNA carrying alternative exon 5 presumably participates with BuChE in scavenging bloodborn inhibitors including drugs of abuse	Works with AChE-E
	AChE-R rare 'readthrough' mRNA. Retaining intron 4 in the	

	open reading frame encodes a novel AChE isoform that upregulates under some physiological conditions including acute stress and exposures to AChE inhibitors. It has been shown to be a monomeric, hydrophilic, soluble form of catalytically active AChE. In hippocampal brain slices, elevated AChE-R was associated with suppressed electrophysiological activity 3 hrs post-treatment with physostigmine. Specific isoform AChEi need to be developed. OR Antisense technology	

Feedback overexpression of AChE alters the balance and levels of AChE isoforms. Dr. Soreq rhetorically asked whether or not it might not be better to develop antisense technology instead of trying to develop a specific isoform AChEi directed against the AChE-R variety. She described how designing an exon specific oligonucleotide to preferentially target exon 6 (AChE-S) or intron 4 (AChE-R) might work. Another approach might be to exploit the instability of the AChE-R.

15.

Research Concepts on Anthrax Vaccination Testing
Presenter: Dr. Jack Melling

Dr. Melling described the various types of anthrax disease expression, including inhalational, cutaneous and intestinal. Testing for the pathogen requires laboratory tests involving smears of blood, cultures and ELISA. Treatment, when possible, is by antibiotics.

Dr. Melling identified three possibilities related to an association between the U.S. anthrax vaccine received during the Gulf War period 1990-1991 and GWI in U.S. troops.

A causal relationship exists between the anthrax vaccine and development of GWI.

Anthrax vaccine may act synergistically with other factors e.g. PB, other vaccines, exposures, pollutants to increase the possibility of developing GWI.

There is no direct relationship between receipt of anthrax vaccine and the development of GWI

Option number one is the easiest condition to replicate and evaluate in a well controlled clinical trial. If a causal relationship did exist between anthrax vaccine and GWI, it could have been based on one or more of the following factors:

The vaccine given to troops in 1990/1991 was defective either in inherent composition or in manufacture

A component of the vaccine other than the Protective Antigen (PA) was responsible. The Anthrax Vaccine Absorbed (AVA) is a 1950's type primitive vaccine that contains several proteins in addition to the PA (30%). All of the proteins are adsorbed to Alhydrogel, which is present as an adjuvant.

The PA component itself is a key factor.

The only batch of vaccine that could be tested would be current, AVA viable vaccines. The batches from 1990/1991, even if available, would no longer be the same as a decade ago.

Dr. Melling reminded the Committee that the US vaccine contained little or no lethal factor while the UK vaccine did contain some lethal factor. He said that the key to the vaccine efficacy was the PA; it is not toxic but is biologically active.

He said that there had been a lot of work trying to purify 95% of PA but that it is a terribly expensive endeavor. Dr. Melling said that NIH and NIAD are working on a study to purify the agent. He said that the VA might want to talk to the NIH and CDC regarding treatment trials.

The Suggested trial design arms were as follows:

- AVA
- Adjuvant (Alhydrogel) alone
- Purified PA + Alhydrogel
- PA alone
- Saline

<u>Considerations:</u>
Double blind, randomized, placebo-controlled, healthy adults, age range to reflect the military population

Discussion:
Dr. Golomb strongly endorsed that idea, noting that randomized trials would be the most definitive approach to resolving outstanding questions about anthrax vaccine safety. Both positive and negative findings relating to long term health outcomes would provide seminal information: the former would permit more reasoned risk-benefit decisions in ongoing anthrax vaccination programs, as well as suggesting a role for these vaccines in

chronic health problems in ill Gulf War veterans. Negative findings, in properly conducted and powered studies, would indicate safety in ongoing vaccination programs, though differences in manufacturing procedures now relative to the Gulf War would leave open questions regarding whether the vaccine, as manufactured then, may have contributed to health problems.

Dr. Nass, from the audience was asked her opinion and said that the people from the postal episode with anthrax were not worked up clinically very well but that they were found to have pleural effusions. The issue of the PA toxicity remains open at this point.

Dr. Golomb noted that changes in anthrax vaccine production methods in 1990, during the ramping up of production prior to the Gulf War, included filter changes (that were not reported to the FDA at the time), from ceramic filters, that trap many proteins and much PA, to nylon filters, which are much less apt to trap proteins. Proper pre-post testing was not performed, but DOD findings have led to estimates that this induced as much as 100-fold increases in PA in the vaccine. Since the US does not routinely measure lethal factor and edema factor entering the vaccine, the existence or magnitude of increases in these factors is unknown. (Of note, there have been two subsequent filter changes by the manufacturer.)

Dr. Melling said the UK had 1/3 of the amount of PA that the US vaccine had.
[BG Note: this may depend on which filter was used at the time. Very large lot differences in potency and reactogenicity have been seen in the US vaccine.]

Dr. Golomb noted that the UK vaccine also had more lethal factor and edema factor than did the US variety -- though this has not been separately tested following each filter change.

Dr. Sushil Sharma, from the audience, who has examined issues related to the anthrax vaccine for the GAO, made three points:
First, from the standpoint of Congress, they are wanting the Committee to put make a final determination of whether the anthrax vaccine did or did not cause problems for veterans, to provide information regarding compensation for Gulf War veterans and for subsequent recipients.

Second, as a result of the anthrax vaccine, what was the opinion of the Committee regarding the Rook theory of Th1-Th2 shift expanding toxic exposure to the human immune system and Simon Wessely's finding of, indeed, higher Th2 levels and mechanisms that might explain it.

Thirdly, another country, which Dr. Sharma would not name, which has reported the highest level of PA has also reported the highest level of illness.

Dr. Golomb added that the study should be designed and powered to look at chronic health problems occurring at a 15% increased rate with power to assess gender

differences. She suggested adherence to GWI criteria (such as those of Fukuda et al) assessed perhaps at 5 years follow-up.

Secondary clinical outcomes suggested to include leading symptoms, measured at baseline, in ill PGWV. She further suggested use of a change score to reduce the variance and enhance power to detect any effect that may occur. If the RCT is adequately powered, a test of difference in mean score for treatment vs. control would be sufficient.
Outcomes to be included:

- Cognitive battery - could include Elithorn maze, grooved pegboard, digit vigilance (validated scales that address attention and psychomotor speed)
- Validated fatigue questionnaire
- Validated pain questionnaire
- Leeds sleep scale
- Multisymptom survey
- Quality of life battery (e.g. SF-36V=veterans version), including subjective overall quality of life.

Dr. Golomb suggested objective markers as secondary outcomes, including:

- Squalene antibody testing, including pre-vaccine (baseline) – and post-vaccine measurement (after each inoculation, and at 1, 6, 12, and 60 months) in all or a subset active treatment and placebo group.
- Biochemical assessments/ immune related elements, such as cytokine profiles
- Archive: plasma, serum, urine at –70 degrees to allow future testing
- DNA samples archived for future testing

Dr. Golomb noted that for patient safety, cost efficiency, and power reasons, a preferable design may be to compare AVA to saline placebo first. If no effect is present, the current vaccine, at least, is safe for use and can be administered. There is no need for the cost of additional subjects, and no need to further delay usage in those who might benefit. If, on the contrary, an effect is present, then the fewest number of subjects were placed at risk in this determination. If follow-up testing is desired to ascertain which elements are relevant, then the mandate of maximally informing volunteers about the risks associated with research participation can be met.

Dr. Pellier said that if his memory served him correctly, very little was understood about the biology of the vaccine. His question was why would we want to expose hundreds of thousands of more people to it without knowing that basic information? He also wanted to know if anyone had looked at IgA to boost the response.

Dr. Melling said that how much protein is known and that CDC will be doing a study looking at the immune response.

Dr. Sharma said not to put too much faith in the CDC studies and that there is an opportunity to do a longitudinal study on those who took the original vaccine.

The goals of such trials would be to evaluate AVA with respect to GWI and to integrate as many as possible of the tests and protocols that RAC-GWVI discussed with the NIH and DoD with the objective of assessing the safety and efficacy of rPA compared with AVA.

Dr. Cherry asked what baseline measures have been taken, and how long would a Th1-Th2 conversion take? The answer was not known.

Mr. Binns asked if cytokine tests should be part of the Committee's recommendations.

Dr. Steele asked if there were any squalene in the new vaccine.

Dr. Golomb noted that reportedly, none is included; but testing for squalene has not been done with the new vaccine. FDA testing of four earlier lots found squalene to be present at 10 to 80 parts per billion, a quite small amount. Whether this is enough to have an effect, in concert with adjuvant; or whether lot to lot variability is such that larger amounts were in other lots, remains unknown.

Mr. Robinson said that he had heard that at Walter Reed Army Hospital they were drawing blood before the anthrax vaccines were being given and after the series.

Dr. Golomb reinforced the need for a saline arm to the trial. What matters is not just whether a given element of the vaccine causes problems, but whether any element of the vaccine causes problems.

Dr. Melling said that he sees two issues that have emerged: 1) to test the current blood samples and 2) to open discussions with NIH and CDC.

Dr. Golomb mentioned that the Dover, Korea and Tripler experiences have shown high levels of acute reactogenicity with the anthrax vaccine, and encouraged long-term follow-up in participants in those studies (both to provide information on the long term health of vaccine recipients overall; and to determine prospectively whether there is a connection between acute adverse responses and chronic health problems, as retrospective studies of Gulf War veterans suggest).

16.

Tokyo Conference on Indoor Air Quality and Health Quality Environmental Factors as Causes of Illness with Possible Treatment Options
Presenter: Dr. William Meggs

Report on the Jan 7-12th, 2003, Japanese Institute of Architecture, Tokyo, Japan

Dr. Meggs attended a conference sponsored by the Government of Japan's Institute of Architecture and the US Government's National Institute of Environmental Health Sciences. The relevance to ill Persian Gulf War veterans was made clear when the issue of possible subtle neurotoxicity and autonomic dysfunction syndromes were discussed. Organophosphate-induced delayed neurotoxicity [OPIDN], Chronic Fatigue Syndrome,

Sick Building Syndrome and MCS as well as GWI have been and continue to be problems faced in several areas of the world. The events of September 11th have added yet another cohort of patients into the fold with syndromes that are the focus of scientific attention.

Pulverized powders of concrete, asbestos, fiberglass, carbon and other toxic elements are finding their way into the lungs of an unwilling population on a daily basis. Metals such as manganese, mercury, lead, chromium, aluminum, nickel and cadmium and volatiles such as benzene, toxic solvents and multiple volatile organic chemicals have become a way of life, and for many a source of chronic illness.

Respiratory illnesses such as rhinosinusitis, asthma, and sub-clinical asthma are on the rise. Musculoskeletal disorders such as myalgias, arthralgias and arthritis are attacking younger people today than they did twenty years ago. Neurological issues such as headache, cognitive dysfunction and constitutional disorders including fatigue and generalized malaise appear to be on the rise.

Subsequent chemical exposures tend to exacerbate CNS disabilities and cognitive disabilities seem to wax and wane with exposures.

Dr. Meggs described the concept of Environmental Medical Units (EMUs) conceived by Dr. Theron Randolph, and opened as clinics from 1966-1974 in the US as clinical tools to evaluate environmental factors in patients with specific diseases. These clinics seek to provide controlled environments, with some degree of control over air, diet, water, and electromagnetic fields, providing places affected persons may go for decontamination and to regain health.

He said that there is a movement in several countries to have more of these clinics worldwide, but in the US they are opposed by organized medicine and third party payers.

He stated that there have been several recommendations from leading US organizations to run some therapeutic trials. Some of the recommending groups have been:
-NAS Sub-Committee on Immunotoxicology, Washington, D.C., 1991
-NRC Workshop on Multiple Chemical Sensitivity, Irvine, CA, 1991
-Expert Panel on Multiple Chemical Sensitivity, ATSDR, 1993
-Exp Approaches to Chemical Sensitivity, EOSI & NIEHS, RUGERS, 1995
-CDC Gulf War Syndrome Meeting, Atlanta, GA,1999

Types of Investigations and questions that are germane to Gulf War Veterans' Illnesses:

What are the effects of environmental factors on specific diseases and syndromes?
What are the effects of sub-acute to sub-chronic exposures to VOCs on Immune function, cognitive function, etc.?
What is the nature of adaptation phenomena?

These are the questions; what is needed to answer the questions may be performance of studies using an Environmental Control Unit (ECU), with the following features:

1. Controlled residential unit
2. Reasonably pristine environment
3. Equipment to produce and monitor environmental exposures
4. Dietary and kitchen facilities
5. Engineering staff
6. Medical staff

Criteria for studying a disease in an ECU:

Clinical experience

Diseases in which chemical exposures are believed to play a role in some patients

Epidemiological association between exposures and disease

Association does not imply causation

However: association implies need for study

Examples of Diseases Evaluated in Environmental Control Units

Respiratory	Asthma, Rhinitis, Sinitis, Pneumonitis
Musculloskeletal	Mucositis, Arthritis, Collagen vascular diseases
Gastrointestinal	Irritable bowel syndrome, Inflammatory Bowel Disease
Dermatological	Dermatitis, Rosacea, Cutaneous Vasculitis
Cardiovascular	Unstable Angina, Hypertension, Arrhythmias, Vasculitis, Recurrent Anaphylaxis
Neurological	Migraine, Seizures
Psychiatric	Bipolar Disorder, Depression, Psychosis

Interpretation of Results: Generalized Adaptation Syndrome

Stage 1 Preadaptation (nonadapted)	Shock Reaction (Acute Reactivity to chemicals)
Stage II Addicted (Adapted) IIa Adapted IIb Maladapted	Tolerance Chronic Illness
Stage III Postadapted (Nonadapted)	Exhaustion

Specific Adaptation Syndrome

Maladaption to a single substance whereby substance is tolerated without acute reaction but there is chronic disease. The elimination of one substance leads to withdrawal symptoms then resolution of chronic disease. The re-exposure to that substance leads to acute reactions.

Chemical Stress Syndrome

Stage 0 -Normalcy	Tolerance of chemical exposures, wellness without symptoms
Stage 1-algia	Sensory Hyper-reactivity, Subjective symptoms associate with chemical exposures (arthralgias, myalgias, etc)
Stage 2- itis	Inflammatory reactions to chemicals (arthritis, myositis, etc)
Stage 3- osis	Fibrosis, Tissue destruction (arthritic deformities, muscle atrophy and necrosis, etc)

Chemical Stress Syndrome
-Dynamic
-Patients move back and forth through the stages
-Exposures drive patients between the stages
    -Eliminating inflammatory chemicals moves patients to lower stages
    -Exposure to inflammatory chemicals moves patients to higher stages

Stage 3-Fibrosis and scarring-is permanent

Multiple Chemical Sensitivity Syndrome
-Unfortunate terminology
-Term coined by physician who only saw patients in Stage 1 of the Chemical Stress Syndrome, sensory hyper-reactivity
-No recognized physical findings - patients not examined
-Extraordinary high incidence of 'occult rhinitis' in patients given the MCS label.

Emphasis
-Exposure to the Chemical Environment induces and exacerbates known problematic syndromes as well as diagnosable valid medical conditions with findings on physical exam and laboratory testing.
-In many cases, these diseases can go into remission with environmental control.

Conclusion
In conclusion, Dr. Meggs reported that much research still needs to be done in this area to define the validity and extent of clinical observations in Environmental Control Units and suggested that EMU could be a valuable tool for evaluating ill Gulf War veterans.

17.

Presentation: Gulf War Veterans Information Service Report (GWVIS)
Presenter: Mr. Steve Robinson & Dr. Robert Haley

Mr. Robinson stated that the Department of Veterans Affairs had just issued the latest Gulf War Veterans Information System report. The report, due November, 2002, was issued January 24, 2003.

He stated that the report prompted numerous questions. What illness conditions are more prevalent among GWV? Are rates of illness higher among the group exposed to the

Khamisiygah incident? There is a need for a professional statistician to address these questions.

He reiterated the importance of DoD providing unit location information to the VA Gulf War veteran's database. He asked what was the status of the Committee's recommendation that these databases be merged.

Mr. Binns noted that the recommendation had been reiterated in the letter to Secretary Principi accompanying the Committee's annual report in December.

Dr. Haley confirmed that incorporation of the unit identification code (which provides location information) was important to research. He also urged that the GWVIS report be expanded to include a table of all diagnosed conditions by ICD-9 code, tracking the rates of conditions by age, sex, deployment status, location data, and relevant exposure plumes.

Dr. Pellier cautioned that in that size undertaking, many results will achieve statistical significance by chance.

18.

RAC-GWVI Recommendations
Presenter: Mr. James Binns

Mr. Binns suggested that the Committee consider formulating recommendations based on the presentations and research reviewed at the meeting. The Committee discussed the various research presented to the meeting and adopted the following recommendations.

With regard to the new research on Gulf War illnesses published since the Committee's last meeting in October, 2002, the Committee:

- notes the significance of these studies in beginning to uncover the possible mechanisms involved in an important category of Gulf War illness that is neurological in nature, for example, the studies sponsored and conducted by the U.S. Army Chemical Defense Institute, on low-level exposures to sarin* and the study sponsored by the National Institute of Environmental Health Sciences and conducted at Lawrence Livermore National Laboratory on the combined effect of low levels of neurotoxic agents*;

- commends the federal agencies involved in this research, and supports the aggressive pursuit and expansion of these lines of research and others directed at understanding mechanisms of injury.

- notes that, in addition to their implications regarding Gulf War illnesses, these discoveries have important implications for the potential development of medical defenses against chemical weapons.

With regard to the ALS study presented by Dr. Nelda Wray, the Committee:

- supports the VA's program of continuing to monitor new ALS cases, particularly in view of the exponential pattern of increase in ALS cases;

- supports VA's ongoing review of past medical history and environmental exposures, particularly in light of anecdotal cases where a later exposure to pesticide occurred shortly prior to an ill Gulf War veteran developing ALS;

- supports additional investigation of rates of other neurodegenerative disease not counted in the study.

With regard to the presentation by Dr. Han Kang, the Committee:

- appreciates the interest of Dr. Kang in the previous recommendations of the Committee regarding the collection of treatment data and the special efforts made by him and LTC Karl Friedl of the U.S. Army Medical Research and Materiel Command, Fort Detrick, MD, to solicit treatment questions from the Committee and to add them to the Longitudinal Health Study of Persian Gulf War Veterans;

- recommends that VA accelerate and complete its review of medical records of all self-reported birth defects, or to conduct clinical exams if no record exists; and that VA make an analysis to determine the rate of confirmed birth defects in ill Gulf War veterans (not just all Gulf War veterans) and in appropriate sub-groups such as by forward vs. rear area location and by severity of illness;

With regard to the presentation by Dr. Tom Finley, the Committee:

- supports continuing research into physiological mechanisms such as balance and pain sensitivity;

- recommends against funding the pending proposal entitled "Prospective study of the functional status of veterans at risk for unexplained illnesses," in view of the recent major British study showing that psychiatric disorders cannot explain illnesses in ill Gulf War veterans*.

With regard to the presentations by Dr. Hermona Soreq, the Committee:

- recommends immediate funding of a study to test for the AChE-R variant form of acetylcholinesterase in coded serum specimens from three groups of veterans: (1) ill Gulf War veterans, from several groups identified in different studies; (2) well Gulf War veterans; (3) well non-deployed veterans.

- if the AChE-R variant is found to be associated with ill veterans, recommends proceeding with clinical trials including required preliminary regulatory toxicology studies. (It was also suggested that an initial one-week study could be conducted without additional toxicologic studies, with the understanding that the full study would still be conducted if the one-week study failed to show improvement.)

19.

RAC-GWVI Work Plan
Presenter: Mr. James Binns

Mr. Binns presented a draft work plan for the Committee.

He said that he was excited to see Dr. Wray become the new head of R&D and would hope that the Committee would be able to expand its relationships with the VA research staff working on GWI and related areas. He also noted the need to continue to develop our relationships with DoD and other government agencies involved in Gulf War illness and related research..

Mr. Binns addressed the issue of researchers and experts that the Committee was interested in hearing from at future meetings.. He appreciated very much the fact that Dr. Soreq had traveled so far to be with the Committee. He also expressed appreciation for the presentations (and travel, in some instances) of Drs. Wray, Kang, Findley and Mr. Phillips, and thanked them all for their presentations.

He welcomed comments or suggestions regarding the work plan draft.

Dr. Steele asked the Committee how they saw their work being produced and provided to others. She asked whether the Committee was just making recommendations and then issuing them to the Secretary when the Committee had reached consensus; or did they see themselves as generating reports like other Committees have done?

Mr. Binns said that this Committee has one difference from other Committees, in that they are not assigned to develop a report and then cease existence. Therefore, by definition, they would be making recommendations over time. However, this is not to say that they cannot make reports or other documents as part of the process.

Dr. Steele then asked Mr. Binns if she was correct in assuming that whenever they have a meeting and have a few recommendations that they will then forward them to the Secretary.

Mr. Binns replied that it would have been wonderful if they had been able to get through everything that they had hoped to have accomplished by the end of last year, and had

been able to produce one comprehensive report, but that they are now where they are and that he does not want further delays in going forward with recommendations.

Dr. Steele said that she thought that the preliminary report worked really well. She said that they were under a time constraint and that they had to get something out by a certain date.

Mr. Binns said that combining the treatment recommendations that Dr. Steele drafted and Dr. Golomb's mechanism recommendations plus the individual research recommendations on the research presented at this meeting would make a nice presentation.

Dr. Pellier said that perhaps one way to address what you are saying, and that he agreed with Mr. Binns on all of his points, would be to plan a set of objectives and put some timetable associated with them so that everyone would know and have a common objective by the next meeting.

Mr. Binns said that that could be part of the Committee's report.

Dr. Steele said that she doesn't want to leave off oil well fires, and other putative exposures, although a dedicated report or set of recommendations may not be needed. She noted that one specific concern was jet fuel. She said that it would be helpful to have some kind of review at least for the Committee members about what is known and what is not known about these other exposures. She said that she feels like there is a lot already done in these areas that might be important for the Committee.

Dr. Golomb said that she would caution against spreading themselves too thinly. Oil well fires, depleted uranium, and infectious diseases were each a topic of a separate RAND report that took about 2 years to produce, involving people who devoted a lot of time and money to doing that. (This was when there was less literature to review.) She said that the Committee does not have the staff to do everything. She encouraged the Committee to focus and prioritize. She observed that she doesn't have any objections to exploring any of the cited areas, or to conducting brief reviews but as the Committee has seen from reviews put out by other groups, cursory reviews can be frankly wrong, and may add little to understanding.

Dr. Steele said that they could borrow from those extensive reports, since it is preexisting information they could do an update and just go to the bottom line. She said she thought that the Committee has not informed itself about whether it thinks that something is important or not.

Dr. Golomb said that she did not think that any of the theorized exposures could be excluded as potentially important and that one of the things that she had hoped to do, which was not on the list of priorities, was to prepare a briefing that the staff had begun to assemble articles for, summarizing both risk ratios for exposure outcomes, and determining approximate attributable risks. You can have something, she noted, that has

a smaller risk ratio but is more prevalent and therefore has a bigger attributable risk, that more veterans' health problems derive from. This may help to define, among remaining topics, which are of greatest priority to explore.

Dr. Steele said that existing epidemiological studies often look like all of the exposures give a certain level of risk.

Dr. Golomb agreed that the only way to examine each area sufficiently to understand its importance would be to conduct a full literature review on each exposure; but the Committee simply does not have the staff to do this and also follow through on its other objectives. This is why prioritization is needed, and apparent attributable risk represents one approach to such prioritization.

Dr. Cherry said that she thought that an intermediate solution might be the following, taking the example of oil well fires. We would like to know something about what possible health outcomes we should be monitoring for people who were exposed to oil well fires. One question could be lung cancer concerns. Should we worry enough to take symptoms questions two years after the event, and what common course should we be following? We could even perhaps invite someone from the outside to come and give a talk to the Committee at one of our meetings.

Mr. Robinson said that he didn't think that the RAND reports, for example, as everyone is now finding out on things like sarin exposures and oil well fires, are the end-all reports they were once touted to be. He said that we cannot depend on their studies to determine if an exposure made people sick or not. He thought that the Committee should be the one to set the priorities. [Note from BG: the RAND reports, including two to which BG contributed, very much did identify AChE inhibitors, including sarin, as a risk factor of significant concern. Mr. Robinson, however, is absolutely right that only an independent reading will be satisfactory -- just as the findings of these RAND reports departed from those of prior reports. Yet again, those new readings took substantial time and effort.]

Mr. Binns said that the experiences of coalition countries, in general, was also on their list of things to explore and that it should still be there for the upcoming year.

Dr. Golomb again expressed concern about the Committee spreading itself too thinly.

Dr. Steele said that there is no deadline.

Dr. Meggs said that perhaps the Committee should generate an interim report at some time describing the things we have discussed. It could describe the treatments, our recommendations and their limitations and whatever else it seems like we should be communicating.

Mr. Binns said that he hoped they would have had a document that would have included the different things that the Committee had talked about yesterday and today, and that they would have been able to go forward with that document before the next meeting.

Dr. Meggs observed that the minutes of the meeting could become a report, if put in the proper format.

Dr. Golomb concurred that the Committee could issue a report instead of, or in addition to the minutes.

Dr. Meggs said very important things that have been discussed at these meetings, that it has been very enlightening, and he thinks that this enlightenment should be communicated in the best way and to the largest audience.

Dr. Cherry said she didn't remember if immunology had been discussed, and she thought that this merited discussion; she would like to be educated in that area. She said that she was also wondering if perhaps the Committee could invite a researcher from the Chemical Defense Research Institute to help the Committee better understand their work.

Mr. Binns said that he thought their work was highly relevant and interesting and that Dr. Wray had made a similar request.

Mr. Robinson stated that US troops are getting ready to deploy right now, and that he does not know whether the Committee wants to step up and do this or not, but that there are certain things that they know ought to be done as a result of the lessons learned from Gulf War I. He said perhaps the Committee would like to come up with a list of recommendations of things we would hope would be done to protect the troops.

Mr. Smithson said that the Committee needed to find out what the status was of the letter that had been sent to the Secretary. He noted that continuing to send letters was useful only if they were reviewed and influenced policy or actions.

Mr. Binns said that the Committee had to discuss things before they could go into a report and that that was an obligation by charter. He said that the lessons learned have been discussed so they could be converted to a recommendation, if that is what the Committee wished to do. However, personally, he did not like the idea of repeating the same thing in a different document. He thought it would be better to keep certain items in their original format, and append them to the report as is.

Dr. Golomb said that in the forthcoming Millennium Cohort Study it sounded like they are not going to include somatic symptoms so that there will not be pre/post-measures of somatic symptoms that could be correlated with exposures. If there was a way for us to verify that it might be an important area for us to make a recommendation for additions to the Kang study.

Mr. Binns asked if there were any other comments on the 'Lessons Learned'?

Mr. Robinson suggested we add Dr. Golomb's recommendation to the Committee's report.

Mr. Binns expressed concern that this might extend beyond the Committee's charter, which is to address health in Gulf War veterans.

Dr. Golomb observed that this was directly relevant to the Committee charter, noting that performing studies to identify which exposures are linked to which outcomes had been difficult following "Gulf War I" because of limitations in the data collected. If we could get the needed pre-post outcome data, coupled with exposure data, from the Millennium Cohort Study, this will dramatically facilitate epidemiological studies that are directly relevant to Gulf War veterans. Such studies may more definitively address the link between selected exposures and outcomes, and may more closely characterize the nature of those outcomes. Such studies may provide more authoritative answers to questions that existing epidemiological studies are poorly able to provide.

Dr. Meggs commented that the Committee's work is not limited to the formal meetings because they can do preliminary data gathering outside of the meeting.

Mr. Binns noted that the Committee has also had teleconferences with experts. In addition to physicians and scientists, Mr. Steve Robinson was in on the call with the group of expert panelists, and having a veteran's perspective was valuable for a scientist to hear. He underscored that the non-scientist members should not shy away from these teleconferences.

Mr. Robinson said that he wanted to add that Mr. Kurt Love had mentioned that the veterans are very concerned that tissue samples be collected, so they may be available for analysis. He noted that the expert panel had also expressed interest in collecting brain samples, and were exploring other important avenues, including genetics.

Mr. Robinson said that Dr. Black, a member of the expert panel noted that materials sent to them were interesting, but that there was still a need to define the character of the problem that Gulf War Veterans are experiencing.

Mr. Smithson said the IOM report on pesticides and solvents will be out in a few weeks, he said. Vol 1 focused on sarin, vaccines, DU and PB. He said that it was important that the Committee be involved, in an official capacity , in reviewing the report and commenting on this to the Secretary, because these reports have a major impact on how GW veterans are compensated.

Mr. Binns said that there was one more recommendation, based upon Committee presentations that were mentioned in his opening remarks and that Dr. Golomb mentioned in her presentation on recent research, and that was the Lawrence Livermore National Laboratories work. He thought it would be appropriate to mention their research and support continuation and expansion of that work.

He also noted that the Chemical Defense Institute, in its briefing to the Committee following the formal part of the October meeting, specifically stated that, if they uncover

new science, and if the current modalities for dealing with that threat are not met by current therapies, then part of their mission is to go on from there to develop new therapies. He said that he thought the goals of the Committee are very much along the same lines. The Chemical Defense Institute has made some very exciting breakthroughs and the Committee ought to be behind them and tell the leadership of the VA and anyone else who will listen that they are doing important work; not only for the GW veteran but for chemical defense in general.

Dr. Golomb suggested that the Committee should frame the recommendation in such a way that they were supporting, or that the Committee strongly endorses, recent work like that of this group, in evaluating the mechanism of chronic persistent problems following low level exposures. She noted that we may not wish to imply that money go to one group, when others may begin to perform or propose work of at least equal value. She said that she thought the idea was to open up the field to even more groups who would want to do similar things.

Mr. Binns said that yes, it should be broadened but that he did not want to leave the specific recommendation that the Chemical Defense Institute and the Lawrence Livermore National Laboratories should get more money to pursue their work out of the report. He said that he thought that it was appropriate for the Committee to specifically support them by name.

20.

PUBLIC SESSION

*** Ms. Venus Hammack** wanted to report to the Committee that in 1994 she was a participant in program at VAMC, North Hampton and Leeds Massachusetts. She said that Dr. Myra Shayevitz and her physician husband thought that Gulf War veterans, according to CNN reports, were ill due to their exposures to dirty occupational environments. Ms. Hammack said that at the time she walked into their clinic she could not think clearly and not even recite her own social security number.

Dr. Shayevitz tried to create a clean environment in a section of the hospital by coordinating with the cleaning crew, the dietician, exercise therapist, respiratory therapist, etc. She said they tried to get all natural linens and to keep the Clorox-based materials away from that part of the hospital in an effort to keep it as free from chemicals as possible.

She said that the husband and wife doctor team wanted patients to try and live in this environment for six months to see it that would alleviate some of their symptoms. Ms. Hammack said that she lived there for four months. Sometimes there were bad withdrawal reactions but everyone was monitored all the time, in case there was a problem.

Ms. Hammack said that she was not claiming that it was a ‘cure’ for GWI but she can say that it did improve the quality of life for those who were there and it lessened the

symptoms she was having. She said from that experience she learned that she had multiple chemical sensitivity. Her own triggers were, she thought, the mass vaccinations and being in the wrong place at the wrong time during low level exposures. She said that they probably built up levels in her body to create a health burden that left her ill for the remainder of the time she was in the Gulf region and up until this day.

She had found out about the Drs Shayevitz program via word of mouth, but when she went to the VA central office they said they had not heard of the study and when they found it they said it hadn't been approved and shut it down. She said that she tried to find other programs and physicians who were interested in alternative medicine and environmental medicine but that they were all doing research and not practice.

She said that these occupational medicine specialists helped her, but she hasn't found any VA or DoD studies or anyone doing research in those areas, and that the Committee should put that on their list and follow-up on that. She said that they should address toxins found in the battlefield and how they affected the Gulf War soldier.

When Ms. Hammack returned to the U.S., she said that road traffic would set her off. She was slowly reintroduced to things at home and to foods to find out what she could and could not tolerate. She said that some people could not even return to their own homes without becoming ill. She related the story of a female veteran who did not pay attention to dietary or exposure guidelines. She said that this person's health condition soon deteriorated.

She said that she is also a bit frustrated because yesterday there were a couple of treatment trials on the table that looked interesting and that some of them were alternative medicine. Ms. Hammack said that she had hoped the Committee would have written up a draft by now, but she heard that since it would only solve one symptom and not be a cure it was not going to be considered. The Committee should know that as an ill veteran when you have improved even one of our lives you have helped all of us. She said that she wanted the Committee to keep that in mind and that she understands that for this Committee this is only a paper war but that what they do write down does matter. She said that their recommendations will still go to Secretary Principi and he will send them forward to R&D and then it will go through their sieves of politics, money and other things, but the more the Committee puts out the greater the chance that something might have a chance of being followed up on as a project.

The Committee's customer, the veterans, who are listening to you, will at least believe that you tried. She thanked the Committee very much for their time and attention.

*** Dr. Richard Van Konnenberg** thanked the Committee for their time and said that he was recently retired from Lawrence Livermore National Laboratory in California. He said he has a PhD in Applied Science and that he has become an amateur in the biomedical sciences during the last six years with a particular interest in Chronic Fatigue Syndrome, and had been trying to develop a basic disease theory from etiology through symptomatology and treatment options and cure.

He said that in his opinion, the cause is a glutathione depletion. He said that he has devised a questionnaire that he sends out to people he finds on the internet and has analyzed more than 100 cases to date spending as many hours on each case as is necessary. He said that he and the patient will jointly work on their case trying one theory and then another. He said that his studies have found that these patients have a lower than normal glutathione level. He said that there are several ways to test for glutathione.

He said levels are low due to a combination of stressors that the person has gone through; physical, chemical, biological such as vaccinations, mental/emotional and for each person the profile is different. He said that together the stressor patterns become synergistic and reduce the levels of the host's glutathione.

Glutathione is important in several roles. It is important in the immune system especially in the Th1 Th2 shift. It is also very important for one pathway in phase two detoxification, and takes care of the free radicals generated in phase one detoxification.

Dr. Konnenberg said that his theory is that glutathione is the basis of the antioxidant enzyme system and that oxidative stress is caused by glutathione depletion. He went on to cite gene expression and amino acid homeostasis as other areas in which glutathione is important. If GWV are found to be deficient in amino acids, those are things that are readily available over the counter without FDA approval for treatment. It can be done orally with undenatured whey protein or from free amino acids. He said he knows of one person who uses suppositories and they can be delivered by injection.

*** Mr. Scott Walker** introduced himself as a former Peace Corps volunteer and a representative of a company which produces cold processed liquid food supplements. He said that they have had reports from some customers that they have helped them achieve a better quality of life. He handed out audio tapes and literature explaining the products which are available.

He said he was offering 20-30 veterans free product to try, in exchange for their letting him know if it helps their symptoms. He cited a case of one veteran who claims that it helped him after taking the product for two months.

*** Ms. Susan Nail** was the next speaker. She said she wanted to thank the Committee for its commitment to the children, America's veterans and future veterans. She said she was impressed by the depth of the reports reviewed and the Committee's comments. She said the Committee was proactive and that as we sat there someone's child was dying. They have gotten shots, pills, and been exposed to harmful things. We need to be able to take care of them and she would like to see more alternative medicine treatments toward that end. Ms. Nail said she liked the stress theory in that when a person is under stress their immune system is down and they are not able to fight off things, and that they can pick things up that will make them sick.

Ms. Nail said she would like to see a list with the differences between the reservists and the regular veterans and see more data altogether. The majority of the veterans are not in VSOs, she said, but the AMA would be a good place to contact them because every doctor who examines anybody could ask if the patient was a veteran and if they were what symptoms they had and then record it. She said that it has taken far too long to get information and that she would have liked to have seen the minutes of the first meeting so she would have known more about this and would not have had to have gone and looked at the charter.

Ms. Nail said that she is the mother of a GWV who came home with symptoms but is now non-symptomatic. She said he was exposed to oil well fires and came home with rashes but is not going to the VA because he went to the Persian Gulf Registry to be tested and all they gave him was pills for depression.

*** Mrs. Alison Johnson** said that she called the dealer for the infrared sauna units in Boulder, Colorado and asked for the bibliography of scientific reports that he used. He faxed it to her and she circulated it to the Committee and public. She said that it showed that a lot of work has been done in Japan, Scandinavia and the Netherlands. She told the dealer, Mr. Bill Johnson, that it would be appreciated if he could do something for the VA in case they wanted to try the unit. She said he then offered a free 2 person unit to the VA of her choice.

Mrs. Johnson said that the levels of toxic chemicals in the fat in the body can be checked pre and post treatment and that Dr. David Root is going to do a sauna detox program with the firefighters from the 9/11 World Trade Center Syndrome cohort. Dr. Bill Meggs, of the RAC-GWVI, is going to go up to see them do the study so maybe he could report back to the Committee what he thinks of this treatment option.

Dr. Golomb asked Ms. Johnson if they were going to do the fat biopsies with the firefighters and if so, did she know what specific chemicals could be tested?

Mrs. Johnson said that there was a whole list of chemicals that could be tested for but that it gets expensive. She said that Dr. William Rea in Texas has done lots of studies like this so she could give him a call and ask him.

Mr. Binns told Mrs. Johnson that he very much appreciated her efforts in securing the free sauna for the VA's use.

Mr. Frank O'Donnell, DoD Deployment Health Support Directorate
(inaudible on audiotape)

Mr. Robinson said that he was not sure but he knew that they were drawing blood before they were given the vaccination.

Dr. Golomb asked if either Mr. O'Donnell or Mr. Robinson would know who would be the right person to contact for the Tripler or Korean or Dover experiences or to find out what was going on in terms of long term health follow-up in those groups?

Mr. Binns thanked Mr. O'Donnell for his and his group's help in arranging the Committee's briefing with the DoD at the October meeting. He explained to the rest of the audience that they were the ones responsible for setting up the Chemical Defense Institute presentation and also the meeting with LTC. Karl Friedl.

*** Mr. Kurt Love** said, regarding the proposed survey, that some of the Committee members are familiar with relational databases issues that might come up from time to time and offered his help in the following way. He said that he constructed a comprehensive questionnaire survey that has been running since 1997 that has 59 questions. He said that once the survey attracted more than 1,000 participants it became increasing harder to separate out all the types of data fields. He said that in his opinion, the best part of the surveys are the people's personal narratives telling about their medical histories, their conditions, the incidents they have witnessed, things they have survived, etc. He did agree that there are a lot of good elements to the yes/no questions as well. He said that he is offering the data that has already been done because it is there and he does not have either the time nor the manpower to go any further with it.

Dr. Steele then asked if Mr. Love asked about treatments in his questionnaire to which he replied that not everyone answers each field and that the comment part is where you will find that. He also said that that is the part that messes up the data. He said that Dr. Steele probably had the most experience with databases as she did the GW study in Kansas so he would like to give it to her.

He also said that additional software would be needed to further extrapolate the information from the database.

Mr. Binns said that while the offer is appreciated and that the Committee would certainly like to see what information he had compiled that he would like to clarify a point and that is that the Committee, per se, it not doing a survey; the VSOs are considering doing one on their own.

Dr. Steele then asked Mr. Love is he would please email her a copy of his survey so that she could take a look at the fields that were included in the questionnaire.

Mr. Love said that it is on his website but that he will send her a personal copy.

*** Mrs. Denise Nichols** said that she would like to see a list of all criteria that the Committee would like to see used by researchers; Khamisiyah veterans locations, unit code, job descriptions, etc. , whatever it is that they think the researchers would need to utilize in order to define their populations. She said that the job description tells a lot about a soldier, whether they were a pilot or a Patriot missile person, and that there may be other factors that haven't been considered.

She said that she would like to see the numbers in all services of females who served and that often times they are forgotten and that they make up 12-13% of the troops which is a significant number.

DU was another thing she asked the Committee to consider on their list of things to do. She said that Dr. Dupropovitch had moved back to the States and that she hoped the Committee would invite him to come and give a talk about his research what has been published in Military Medicine on DU found in the urine and its associated health consequences.

Another recommendation she said she had shared with Mr. Binns and Dr. Pickett and that should be passed on was an article that came out January 29th regarding a newly discovered cellular process that helps cells respond to DNA damage caused by radiation, environmental toxins, novel self-activating biochemical mechanisms that may lead to new cancer prevention and treatment strategies. She said it was from St. Jude's researchers and from the ASCRIB newswire. She said that it is something important regarding DNA damage in the genes.

Mrs. Nichols said that yet another item is dental research, that has already been mentioned by Dr. Nass. Fillings come out, teeth break off and come out; something has got to be done about all these thousands of people who have probably lost their teeth just like Venus and she and many, many others we know already have. This is a huge concern that no one is looking at on our behalf. Unless you are covered 100% you will not be seeing a VA dentist and you won't get to see one even then till your claim has been processed-so you won't even know about the problem; but if you can't chew your food and you don't have money to see a dentist then you really have a serious health problem.

Dental insurance can be quite expensive on the outside and we cannot afford it. I have already lost quite a few teeth; broken off at the gumline. Dr. Doug Rokke has lost quite a few teeth, and Dr. Nass knows many more of us who have the same problem. You have got to show something to the Secretary about this issue; you have got to show something to the veterans. You are doing really good work but the veterans are still not feeling any better. You have to communicate better. Minutes should be number one. You have got to have those minutes available so that they can tap in too. A summary of the recommendations that you are presenting is needed; it may not be in the final form that you will send to the secretary but the information needs to go to those veterans who have pushed so hard to be heard, to keep bills moving, to keep legislation from being enacted that would harm veterans and their claims.

She said that she has some cognitive damage and that she needs some extra time to read materials. Materials that are prepared for a meeting and are passed to the Committee before the meeting should also be provided to the public. She asked why that could not be done? She said that some members of the public are doctors and medical people or have educated themselves in these issues and they want to know what you are looking at.

She said that that would also be a way to spur some interest in what the Committee is doing.

She said that the public needs to see what research the Committee is going through and what is passed to the Committee. She is pleased that Dr. Wray is the new head of R & D, but the public needs to know what she and Dr. Golomb are doing. What emails are they passing around. She asked what was so secret about them and wanted to know why the public couldn't have an edited version? She said that the public wants to know what the Committee is doing and be able to feed into their work. She thanked the Committee and that ended the Public Comment session for day two.

Closing Statements:
Mr. Binns thanked Ms. Nichols and the others for their comments; and thanked those who have sent materials during the year stating that he thought that at least half of the materials circulated to members of the Committee originate from the public. He also thanked Dr. Soreq for coming to Washington to attend the meeting and for staying as long as she did, as well as for her presentations which have offered hope by sharing treatment protocols and experiences with antisense technology in the myasthenic patient.

Mr. Binns said that although progress has not been as fast as he, the Committee and veterans might have wanted that he was pleased that they have found people in the outside world at places like the Chemical Defense Institute, Ben Gurion University, the VA, DoD and others who are committed in their research efforts.

He stated that the next meeting of the RAC-GWVI will be June 16 and 17 in Washington.

Mr. Binns adjourned the meeting

Appendix A:
Antibiotic Therapy Trial (ABT): Doxycycline Treatment of Gulf War Veterans' Illnesses: A VA/DoD Cooperative Study.
Presenter: Dr. Nelda Wray, Chief, VA Research and Development Officer

Appendix B:
Exercise Behavior Therapy Trial (EBT): A Multi-center Trial of Cognitive Behavioral Therapy and Aerobic Exercise for Gulf War Veterans' Illnesses: A Veterans Affairs/Department of Defense Cooperative Study
Presenter: Dr. Nelda Wray, Chief VA Research & Development Officer

Appendix C:
Occurrence of Amyotrophic Lateral Sclerosis (ALS) Among Gulf War Veterans.
Presenter: Nelda P. Wray, MD, MPH, Chief Research & Development Officer

Appendix D:
National Health Survey of Gulf War Era Veterans and Their Families Phase III.
Presenter: Nelda P. Wray, MD, MPH Chief VA Research & Development Officer

Appendix E:
New Research Update.
Presenter: Beatrice Golomb, MD, PhD

Appendix F:
Research at Washington, D.C. War-Related Illness and Injury Study Center (WRIISC)
Presenter: Dr. Han Kang, Director of WRIISC, Washington, D.C.

Appendix G:
Research at the New Jersey WRIISC
Presenter: Dr. Tom Findley, Director of Research, NJ WRIISC

Appendix H:
EN101 Antisense Drug
Presenter: Dr. Hermona Soreq, the Hebrew University of Jerusalem

Appendix I:
Treatment Research Concepts
Presenter: Dr. Lea Steele

Appendix J:
Research Recommendations; Ideas for Discussion
Presenter: Dr. Beatrice Golomb

Appendix A

Doxycycline Treatment of Gulf War Veterans' Illnesses: A Veterans Affairs Cooperative Study

Nelda P. Wray, M.D., M.P.H.
Chief Research and Development Officer
Department of Veterans Affairs
February 3, 2003

1

Doxycycline Treatment of Gulf War Veterans' Illnesses: A Veterans Affairs Cooperative Study

- VA PI: Sam Donta, M.D. (Boston VAMC)
- DoD PI: Charles Engel, M.D. (Walter Reed Army Medical Center)

2

Doxycycline Treatment of Gulf War Veterans' Illnesses: A Veterans Affairs Cooperative Study

- Some scientists suggested that some symptoms in Gulf War veterans could be due to infection with *Mycoplasma*
- Mycoplasma infection responds to doxycycline treatment
- Some anecdotes suggested that these symptoms could be improved, empirically, with long-term doxycycline treatment
- Goal of study: To conduct a randomized, double-blinded, controlled trial to determine if doxycycline treatment for 12 months would improve functional status and/or chronic symptoms in Gulf War veterans

3

Doxycycline Treatment of Gulf War Veterans' Illnesses: A Veterans Affairs Cooperative Study

- Project period: April 1999-November 2001
- Jointly funded by VA and DoD
- Doxycycline and placebo donated by Pfizer Pharmaceuticals
- Conducted at 26 VAMC and 2 DoD hospitals
- Testing for *Mycoplasma* performed at University of Texas at San Antonio, by Joel Baseman, Ph.D.

4

Eligibility Criteria

- At least 2 of the following at screening:
  - Fatigue
  - Musculoskeletal pain, involving 2 or more parts of body
  - Cognitive problems
- Symptoms had to begin after August 1990
- Symptoms had to last more than 6 months
- Score of less than 40 on Physical Component Summary (PCS) of MOS Short Form-36V (V/SF-36) (range 0-100; higher scores are better)
- Positive PCR test for one or more *Mycoplasma* species

5

Exclusion Criteria

- Symptoms were attributable to a diagnosed medical condition
- Allergy to doxycycline
- Previous treatment with doxycycline for more than 6 months since onset of symptoms
- Treatment with certain antibiotics for more than one month in previous year
- History of severe psychiatric illness
- Active substance abuse in previous 2 years

6

Treatment Protocol:

- Patients randomly assigned to 200 mg doxycyline per day or placebo
- Treatment course of 12 months
- Patient assessments at 3, 6, 9, 12, and 18 months
- Doxycyline blood levels determined at 6 and 12 months
- PCR tests for *Mycoplasma* species at 6, 12, and 18 months

7

Primary Health Outcome Measure

- Physical Component Summary (PCS) of MOS SF-36
- Primary endpoint was the proportion of patients who showed a 7 point or greater increase in PCS at 12 months

8

Secondary Health Outcome Measures

- Reduction in pain symptoms (McGill Pain Questionnaire)
- Reduction in fatigue (Multidimensional Fatigue Inventory)
- Reduction in cognitive symptoms (Cognitive Failures Questionnaire)
- Improvement in PCS score of V/SF-36, as a continuous measure
- Improvement in score on Mental Component Summary (MCS) of V/SF-36, as a continuous measure
- Conversion to negative PCR test for *Mycoplasma* species

Enrollment of Patients

- 2, 712 Gulf War veterans screened
- 2,134 veterans met inclusion criteria
- 1,565 veterans had a score of less than 40 on PCS
- 1,387 veterans were screened for *Mycoplasma*
  - 541 (39%) were positive for one or more species
- 491 patients agreed to be randomized into the trial
  - 245 to doxycycline group and 246 to placebo group
- 411 patients (84%) completed PCS at baseline and 12 months (199 doxycyline; 212 placebo)

Baseline Characteristics of Patients

- Mean age 41 years
- 86% male
- 63% Caucasian
- 72% full-time employed
- 84% reported all three symptoms
- Mean score on PCS of 30.5 at baseline (this score is 2.5 standard deviations below the mean of the general US population)

Primary Outcome Measure: Results at 12 Months

- At 12 months, no difference in the proportion of veterans with 7 point or greater increase in PCS:
  - Doxycycline group (18%)
  - Placebo group (17%)

Secondary Outcome Measures: Results at 12 Months

- No differences at 12 months between doxycycline group and placebo group on:
  - Reduction in pain symptoms (McGill Pain Questionnaire)
  - Reduction in fatigue (Multidimensional Fatigue Inventory)
  - Reduction in cognitive symptoms (Cognitive Failures Questionnaire)
  - Improvement in PCS score of V/SF-36, as a continuous measure
  - Improvement in MCS score of V/SF-36, as a continuous measure

Conversion to Negative Blood Test for *Mycoplasma* Species

- Proportion of patients who were *Mycoplasma* negative increased throughout study period in both doxycycline and placebo groups:
  - 6 Months: 55% negative in doxycycline group; 58% negative in placebo group
  - 12 Months: 77% negative in doxycycline group; 75% negative in placebo group
  - 18 Months: 90% negative in doxycycline group; 87% negative in placebo group
- No correlation, at any time point, between negative *Mycoplasma* status and treatment outcome, as judged by the primary outcome of improved score on PCS

Overall Conclusions of Doxycycline Study

- Doxycycline was no more effective than placebo in improvement of functional status and chronic symptoms in Gulf War veterans.
- This study casts doubt on the hypothesized relationship between *Mycoplasma* infection and chronic symptoms in Gulf War veterans.

Appendix B

A Multicenter Trial of Cognitive Behavioral Therapy and Aerobic Exercise for Gulf War Veterans' Illnesses: A Veterans Affairs Cooperative Study

Nelda P. Wray, M.D., M.P.H.
Chief Research and Development Officer
Department of Veterans Affairs
February 3, 2003

1

A Multicenter Trial of Cognitive Behavioral Therapy and Aerobic Exercise for Gulf War Veterans' Illnesses

- Study Co-Chairs:
  - Sam Donta, M.D. (Boston VA Medical Center)
  - Charles Engel, M.D. (Walter Reed Medical Center)
  - Daniel Clauw, M.D. (Georgetown University)

2

A Multicenter Trial of Cognitive Behavioral Therapy & Aerobic Exercise for Gulf War Veterans' Illnesses

- Symptoms in some ill Gulf War veterans resemble chronic fatigue syndrome (CFS) and fibromyalgia (FM)
- Cognitive behavioral therapy (CBT) and aerobic exercise (AE) have been effective in treatment of symptoms in CFS and FM in civilians
- Goal of study: To conduct a controlled clinical trial to determine if CBT or AE would improve functional status and/or chronic symptoms in Gulf War veterans

3

A Multicenter Trial of Cognitive Behavioral Therapy & Aerobic Exercise for Gulf War Veterans' Illnesses

- Project period: April 1999-September 2001
- Jointly funded by VA and DoD
- Conducted at 18 VAMC and 2 DoD hospitals

4

Eligibility Criteria for Gulf War Veterans

- At least 2 of the following at screening:
  - Fatigue that limited usual activity
  - Musculoskeletal pain, involving 2 or more regions of body
  - Cognitive symptoms, including memory, concentration, or attention difficulties
- Symptoms had to begin after August 1990
- Symptoms had to last more than 6 months
- Score of less than 40 on Physical Component Summary (PCS) of MOS Short Form-36V (V/SF-36) (range 0-100; higher scores are better)

5

Exclusion Criteria

- Clearly-defined disease that explained symptoms
- Health condition precluding use of CBT or AE
- Self-reported ongoing, regular aerobic exercise
- Concurrent enrollment in another clinical trial
- Pregnancy
- History of severe psychiatric illness
- Active substance abuse in previous 2 years

6

Treatment with CBT or AE

- Treatment for 12 weeks
- Cognitive behavior therapy
  - 12 group sessions that were 60-90 minutes long
  - Groups included 3 to 8 patients
  - Goal: to learn behavioral skills to improve physical functioning, gradually and safely
- Aerobic exercise
  - Weekly one-hour sessions with exercise therapist, for 12 weeks
  - Goal: to increase activity level, by setting intensity of exercise based on level of patient's symptoms
  - Patients instructed to exercise at least 2 or 3 times a week during treatment phase and during follow-up period

7

Primary Health Outcome Measure

- Physical Component Summary (PCS) of MOS SF-36
- Primary endpoint was the proportion of patients who showed more than a 7 point increase in PCS at 12 months
- Assessment at 3, 6, and 12 months

8

Annual Incidence Rate of ALS

- Rate of ALS expressed as number of confirmed ALS cases per year per 100,000 persons
- Rates age-adjusted
- Compared to non-deployed ALS cases, Gulf War ALS cases were:
  - Younger
  - More likely to be Caucasians
  - More likely to be Reserve/National Guard
  - More likely to be Army

Annual Incidence Rates of ALS

- Overall rate: 0.43 cases per 100,000
  - 107 cases in 2,482,333 veterans
- Gulf War veterans: 0.67 cases per 100,000
  - 40 cases in 696,118 GW veterans
- Non-deployed veterans: 0.35 cases per 100,000
  - 67 cases in 1,786,215 in ND veterans
- Risk ratio: Gulf War veterans compared to non-deployed veterans: 1.92 (95% CI=1.29, 2.84)
- Risk ratio in:
  - GW Air Force troops vs. ND Air Force troops (RR=2.68)
  - GW Army troops vs. ND Army troops (RR=2.04)

Annual Incidence Rates of ALS- Sensitivity Analysis

- Risk ratio of Gulf War veterans, compared to non-deployed veterans, was re-calculated three different ways:
  - Using stricter diagnostic criteria
  - Including only cases with symptoms onset after July 31, 1991
  - Using self-reported deployment status
- Each of these analyses found significantly increased risk in Gulf War veterans

VA Response to ALS Study

- In December 2001, Sec. Principi gave service connection for ALS in veterans who served in Operations Desert Shield/ Desert Storm
- VA contacted Gulf War veterans in this study to help expedite claims for disability benefits
- Manuscript now in review by a journal (revisions have been submitted)
- Analysis of interview data is underway on possible risk factors (family history, military occupation, injuries and trauma, and exposures to hazardous chemicals)
- Ascertainment of cases of ALS is continuing in Gulf War veterans and controls diagnosed after August 1, 2000

VA Continues to Investigate ALS

- 20-year study of incidence and mortality due to ALS in all veterans in Texas (Houston VAMC; started 2001)
- National Registry of Veterans with ALS- identification and interviews of all ALS cases diagnosed in VA hospitals (Durham VAMC; started 2002)

BACKGROUND SLIDE

Determination of Deployment Status

- Deployment to Gulf War based on records of Defense Manpower Data Center (DMDC)
- 15 cases: self-report was different from DMDC
  - 12 cases: DMDC said non-deployed; self-report said Gulf War
  - 3 cases: DMDC said Gulf War; self-report said non-deployed
  - Supplemental data analysis performed, using self-reported deployment status (according to self-report, 49 Gulf War cases and 58 non-deployed cases)

Appendix D

National Health Survey of Gulf War Era Veterans and Their Families Phase III: Medical Evaluations

Nelda P. Wray, M.D., M.P.H.
Chief Research and Development Officer
Department of Veterans Affairs
February 3, 2003

1

National Health Survey of Gulf War Era Veterans and Their Families

- Study Co-Chairs:
- Han Kang, Dr.,P.H.
- Seth Eisen, M.D.
- Frances Murphy, M.D.

2

National Health Survey of Gulf War Era Veterans and Their Families Phases I and II

- Purpose: To compare the health status of a representative sample of 15,000 Gulf War veterans and 15,000 non-deployed veterans
- Self-report survey by mail and telephone
- Compared to non-deployed veterans, Gulf War veterans reported increased frequency of:
  - 48 of 48 symptoms
  - Significantly higher frequency of hospitalizations and clinic visits in the previous 12 months

3

National Health Survey of Gulf War Era Veterans and Their Families Phase III: Medical Evaluations

Goal: To determine the prevalence of several illnesses in a representative sub-sample of veterans and their families through comprehensive medical and psychiatric examinations

4

Phase III: Study Population and Methods

- Study population: random selection of veterans who participated in Phases I and II (4,879 subjects were invited to participate in Phase III)
- Exams performed in 1998-2001 at 16 VA Medical Centers
- Medical examinations:
  - General physical, neurological, and gynecological exams
  - Structured psychiatric interviews
  - Standardized neuropsychological testing
  - Standard blood and urine tests
  - Pulmonary function tests
  - Nerve conduction studies

5

Study Population Examined in Phase III

- 1,061 Gulf War (GW) veterans (53% response)
- 1,128 non-deployed (ND) veterans (39% response)
- Degree of non-response bias was quantitatively similar in GW and ND veterans, in terms of:
  - Demographics
  - Military service
  - Self-reported health conditions at time of Phase I survey

6

Demographics of Veterans Participating in Phase III (* indicates significant difference)

- Gulf War veterans
  - Mean age of 30.9 years in Jan. 1991*
  - 78% male
  - 20% African-American*
  - 68% had 12 or fewer years of education*
  - Mean income of $46,800
  - 86% enlisted ranks*
  - 65% Army
  - 35% active-duty in 1991
- Non-deployed veterans
  - Mean age of 32.6 years in Jan. 1991*
  - 78% male
  - 16% African-American*
  - 58% had 12 or fewer years of education*
  - Mean income of $52,000
  - 80% enlisted ranks*
  - 63% Army
  - 36% active-duty in 1991

7

Primary Physical Health Outcomes

- Chronic fatigue syndrome
- Fibromyalgia
- Peripheral neuropathy
- Physical Component Summary (PCS) of Medical Outcomes Study Short Form-36

8

Secondary Physical Health Outcomes

- Skin conditions
- Diabetes
- Hepatitis
- Hypertension
- Thyroid disorders
- Obstructive lung disease
- Arthralgias
- Dyspepsia

Primary Physical Health Outcomes

Outcome	Gulf War veterans (%)	Non-deployed veterans (%)	P-value	Adjusted P-value
Chronic fatigue syndrome	1.6%	0.1%	<0.0001*	<0.0001*
Fibromyalgia	2.0%	1.2%	0.19	0.04
Peripheral Neuropathy	2.8%	4.0%	0.27	0.92
PCS on SF-36 (range 0-100)	49.3	50.8	0.0037**	<0.0001**

*statistically significant at 99.3% level
**statistically significant at 99.3% level, but not clinically significant

Secondary Physical Health Outcomes

Outcome**	Gulf War veterans (%)	Non-deployed veterans (%)	P-value	Adjusted P-value
Group 2 skin conditions***	34.6%	26.8%	0.0054*	0.02*
Dyspepsia	9.1%	6.0%	0.05*	0.01*
Hypertension	9.1%	12.6%	0.07	0.59

*Statistically significant at 95% level
**Note that none of the other secondary physical health outcomes had significant differences.
***Only two specific skin differences were increased in Gulf War veterans: atopic dermatitis and warts.

Primary Mental Health Outcomes

- Cognitive dysfunction
  - Defined as low score on at least one of seven cognitive domains on neuropsychological tests
  - Low score defined as more than 1.5 standard deviations below the mean score
- Post-traumatic stress disorder (PTSD)
- Mental Component Scale (MCS) of Medical Outcomes Study Short Form-36

Secondary Mental Health Outcomes

- Major depression
- Alcohol dependence
- Anxiety disorders, other than PTSD
- Psychotic disorders
- Bipolar disorder
- Several other psychiatric diagnoses
- One or more concurrent mental disorders

Primary Mental Health Outcomes

Outcome	Gulf War veterans (%)	Non-deployed veterans (%)	P-value	Adjusted P-value
Cognitive dysfunction	35.8%	38.1%	0.42	0.99
PTSD (onset after 1/1/91)	8.0%	2.8%	0.0001*	0.0001*
MCS on SF-36 (range 0-100)	50.0	53.7	0.0001**	0.0001**

*Statistically significant at 99.3% level
**Statistically significant at 99.3% level, but not clinically significant

Secondary Mental Health Outcomes (Onset after January 1, 1991)

Outcome	Gulf War veterans (%)	Non-deployed veterans (%)	P-value	Adjusted P-value
Major depression	15.5%	11.2%	0.03*	0.16
Alcohol dependence	6.8%	4.1%	0.05*	0.41
Anxiety disorders	5.8%	2.4%	0.01*	0.002*
Bipolar disorder	1.0%	<0.1%	<0.0001*	<0.0001*
One or more mental disorders	29.1%	17.1%	0.0001*	<0.0001*

*Statistically significant at 95% level

Health Outcomes in Spouses

- Study population
  - Spouses were examined who were legally married to veterans at time of Phase III study
  - Veterans had to participate in Phase III exam
  - 490 spouses of Gulf War veterans examined
  - 537 spouses of non-deployed veterans examined
- Same primary and secondary physical and mental health outcomes in spouses, as in veterans
- No significant differences in rates of primary and secondary outcomes in two groups of spouses

Birth Defects in Children of Veterans: Preliminary Analysis

- Study population:
  - Veterans had to participate in Phase III exam
  - Children of veterans, who were born after July 1, 1991
  - Children received full pediatric examination in Phase III
- Number of children who participated in Phase III
  - 289 born to male Gulf War veterans
  - 100 born to female Gulf War veterans
  - 261 born to male non-deployed veterans
  - 123 born to female non-deployed veterans
- No significant differences in rates of birth defects in children of Gulf War veterans, compared to children of non-deployed veterans

Summary of Findings of Phase III

- Compared to non-deployed veterans, Gulf War veterans have an increased risk of:
  - Chronic fatigue syndrome (odds ratio of 40.6)
  - Post-traumatic stress disorder (odds ratio of 3.2)
  - Additional mental disorders, such as anxiety disorder or one or more concurrent mental disorders
- Exclusive of the disorders above, the physical health of Gulf War veterans is similar to that of non-deployed veterans.

Appendix E

Review of Recent (and recently identified) Gulf War Research

B. Golomb, MD, PhD

R 1

1. Physiological Effects of AChEi

2. Gulf War Veteran Characteristics

3. Pesticide Exposed Person Ch's

4. ACh Agonists for Treatment?

R 2

I. Physiological Effects of AChEi (alone and in combination)

R 3

Physiological Effects: Preview

EFFECTS OF ACHEI ALONE

- Lo level DFP -> delayed/persistent brain effects
- Lo level sarin -> delayed/persistent brain effects
- Lo level sarin -> T-cell resp. changes

INTERACTIONS & EFFECTS OF INTERACTIONS

- Pesticides increase entry of later OP to brain
- Restraint stress enables effects of low level chemicals
- Exercise potentiates effects of lo level sarin, PB
- Heat potentiates effects of lo level sarin

R 4

DFP on AChR and Memory

Conclusion: Rats exposed to low-level DFP for two weeks showed

- Protracted reductions in AChR in certain brain regions;
- Protracted working memory impairment
- This impairment was reversed with nicotine treatment

Stone JD et al 2000. Brain Res 882 (1-2): 9-18.

R 5

DFP on AChR and Memory

Exposure: DFP 0.25mg/kg for 2 weeks

nAChR reduced: specific types: epibatidine and AFDX-384, much more than QNB

Stone JD et al 2000. Brain Res 882 (1-2): 9-18.

R 6

Sarin Impairs T-cell Responses

Conclusion:

Inhaled low level sarin reduces T-cell function/ responsiveness in rat spleen, inducing immune suppression, 1 day after exposure completed.

This is mediated through the autonomic nervous system: Ganglionic blockers inhibit it.

Kalra R et al 2002. Toxicol & Appl Pharmacol 184: 82-87.

R 7

Sarin Impairs T-cell Responses

Subjects: Male Fischer 344 rats, 8 weeks old

Exposure: Sarin, 0.2 & 0.4 mg/m2 for 1h/d for 5 or 10 days.

Kalra R et al 2002. Toxicol & Appl Pharmacol 184: 82-87.

R 8

Sarin Impairs T-cell Responses

Outcomes Suppressed/Inhibited:

- Antibody-forming cell (AFC) assay (AFC/10^6 spleen cells): Anti-sheep RBC antibody-forming cell response of spleen cells

- T-cell proliferative responses in spleen in response to challenge: (to Concanavalin A & Anti-ab-T cell receptor (TCR) antibody)

- Intracellular calcium rise following treatment with mouse anti-rat-ab-TCR mAb followed by goat antimouse IgG (2nd antibody)

Outcomes Not Affected:

- %B :%T cells: Lymphocyte subpopulations in spleen

Kalra R et al 2002. Toxicol & Appl Pharmacol 184: 82-87.

R 9

Low Dose Sarin Impairs T-cell Responses

Comment: These concentrations of sarin affected AChE regionally but not in total brain.. REGION SPECIFIC EFFECTS.

Comment: Cortisone levels of sarin treated rats were markedly lower.

- "Not related to" activation of hypothalamic-pituitary-adrenal (HPA) axis.

- Could be helped by HPA suppression, or depend on lack of activation (since cytokine-mediated inflammation can increase BBB disruption; and steroids are antiinflammatory)

Comment: PreRx w/ ganglionic blocker chlorisondamine stopped inhib effects of sarin on spleen cell prolif. in response to conA & antiTCR ab's

Mediation of this through autonomic ganglia serves as a reminder that peripheral effects of AChEi can occur in domains (e.g. cytokines) that have central implications

Kalra R et al 2002. Toxicol & Appl Pharmacol 184: 82-87.

R 10

Sarin ± Heat

Conclusion: Repeated low level exposure to sarin - at levels that would not be noticed clinically - led to persistent & delayed changes in cholinergic receptor subtypes that may be related to memory loss and cognitive dysfunction. Some occurred only in the context of concomitant "heat stress" (32°C)

- Delayed decrease in M1 receptors*, sarin w/ or w/o heat: noted at 30 days & not 1 day after exposure

- Persistent increase M3 receptors: only if sarin & heat.**

- Increase brain mRNA for: IL-1ß, TNF-alpha, IL-6 (dose dependent)

Hendersen RF et al 2002, Response of rats to low levels of sarin, Toxicol & Appl Pharmacol 184: 67-76

R 11

Sarin ± Heat

Subjects: male Fischer 344 rats, 10-13wks

Exposure: 0, 0.2, 0.4mg/m3 of sarin for 1h/d for 1, 5, or 10 days; normal (25°C) or "heat-stressed" (32°C). No signs of sarin toxicity.

LCt50 in rats is 220mg/min/m3. 1/10 of LCt50 is 0.4mg/m3 for 60min. (24mg/min/m3). Subclinical levels. No signs observed w/ pilot to 0.8mg/m3 for 1h

Observations: 1d and 1 mo after exposures

Hendersen RF et al 2002, Response of rats to low levels of sarin, Toxicol & Appl Pharmacol 184: 67-76

R 12

Sarin ± Heat

Findings:

- Delayed decrease in M1 receptors*, sarin w/ or w/o heat: noted at 30 days & not 1 day after exposure

- Persistent increase M3 receptors: only if sarin & heat.**

* Frontal cortex, anterior olfact nucleus, hippocampus

** Frontal cortex, olfactory tubercle, ant nucleus, striatum

Hendersen RF et al 2002, Response of rats to low levels of sarin, Toxicol & Appl Pharmacol 184: 67-76

R 13

Sarin / PB + Exercise

Conclusion: Exercise increases the effect of sarin and PB on the following, and may amplify the delayed toxic effect of sarin and PB in specific tissues of mice.

- muscle and nerve AChE

- platelet NTE: OPI DN-related

- spinal cord MDA: oxidative injury

- plasma CK: muscle injury

RER (CO_2/O_2) also affected: PB worsened S+E

Husain K, Somani S 2003. Delayed toxic effects of nerve gas sarin and pyridostigmine under physical stress in mice. J of Burns 2(1):2

R 14

Sarin / PB + Exercise

Subjects: Adult male NIH Swiss mice. 15/group.

Exposures: All combinations of:

- E = Exercise: for 10 weeks

- S = Sarin 0.01mg/kg sc: in 5th & 6th week

- P = PB 1.2mg/kg po: in 5th & 6th week

Timecourse:

- 5 sacrificed for biochem after 10 weeks

- 10 not sacrificed, used for physiological measures (e.g. RER)

- Doesn't really distinguish delayed vs persistent effects.

Husain K, Somani S 2003. Delayed toxic effects of nerve gas sarin and pyridostigmine under physical stress in mice. J of Burns 2(1):2

R 15

Sarin / PB + Exercise

Outcomes:

- Respiratory Exchange Ratio (RER): Treadmill + Oxyscan to measure VCO_2/VO_2: (average per day then per week)

- CK: in plasma

- BChE: in plasma

- AChE: in platelet, triceps muscle, striatum (tissue extract)

- NTE: in tissue or platelet (tissue homogenate or platelet extract)

- Malondialdehyde (MDA) for lipid peroxidation: in sciatic nerve and spinal cord (tissue homogenate)

- CK in plasma (index of muscle destruction)

Husain K, Somani S 2003. Delayed toxic effects of nerve gas sarin and pyridostigmine under physical stress in mice. J of Burns 2(1):2

R 16

Restraint Stress + Low Level Chemicals

Conclusion: Stress plus low dose chemical combination produces effects that don't occur with either stress or low dose chemicals alone (PB, DEET, and permethrin)

- Significant BBB disruption: region specific
- Neuronal cell death: ~30-40% ¯surviving Nns
- Decreased M2 receptors: 20-25%¯ in forebrain

"which could relate to the neurological sx reported by PGW veterans".

Abdel-Rahman et al. Neurobiology of Disease 2002 10: 306-326

R 17

Restraint Stress + Low Level Chemicals

Subjects: 200-250 gm male Sprague Dawley rats

Exposures: 28 days of:

- PB: 1.3mg/kg/d po
- DEET: 40mg/kg/d dermal
- Permethrin: 0.13mg/kg/d dermal
- Restraint Stress: 5 min/d (below level leading to cortisol release)

R 18

Restraint Stress + Low Level Chemicals

Stress + low dose chemicals (but not S or L alone) led to:

- BBB disruption: selected regions only
- Neuronal cell death: C,D,T,H, & other areas (conspicuous -- 27-40% redux in surviving Nns, 4-10% of Nns dying)
- Decreased forebrain M2-AChR (19-25%) and AChE activity

C=Cingulate, D=Dentate, T=Thalamus, H=Hypothalamus.

Abdel-Rahman et al. Neurobiology of Disease 2002 10: 306-326

R 19

Restraint stress + low level chemicals

Measures:

- BBB: iv HRP 135mg/kg; immunostain for HRP with HRP abs; iv EBA with EBA immunostaining
- Neuronal Degeneration: Forebrain viewed: Glial fibrillary acidic protein 1:10000; and endothelial barrier antigen. Silver staining to unequivocally detect neuronal degeneration.
- Surviving & dying neurons: Measured in cingulate, dentate, lateral dorsal thalamus, dorsomedial nucleus of hypothalamus
- M2 AChR: homogenize forebrain tissue, use labeled m2-selective ligand [3H]AFDX384

Brain Areas: (Prev shown to be BRAIN REGION SPECIFIC)

Dentate: gives input to hypothalamus

Hypothalamus: e.g. stress response, temp/sleep regulation...

Cingulate Cx: cortical focus of limbic system

R 20

No Effect of Sarin on Basal Temperature or Activity

Conclusion: coexposure of rats to low-dose sarin and heat stress did not affect median temperature or activity of rats.

Conn CA et al 2002. Toxicol & Appl Pharmacol 184: 77-81.

R 21

Sarin: No change basal temperature & activity

- Subjects: Male Fischer 344 rats, 10-13 weeks old randomized by wt into 3 exposure groups
- Exposure: control; low-dose sarin; high dose sarin. (Nose-only exposure, animals placed in restrainer by nose-hole of exposure chamber for 1h to 0, 0.2, 0.4mg/m3 for 1, 5, or 10 days). 25° or 32°.
- Temperature: intraabdominally implanted temperature-sensitive radiotransmitters. Core temp. proportional to frequency emitted.
- Activity: Change in position of transmitter relative to an antenna under the cage is recorded as an activity pulse.
- Comment: Median temperature & activity used (may fail to capture variability). Also if 2nd of 3 10' measures deviated, it was replaced by ave of 1st and 3rd. Used 2 of 4 day/night cycles (night=dark & day = light periods).

"Basal"; did not assess response to challenge.

- Repeated Measures analysis: by #days, sarin conc, and temp.

Conn CA et al 2002. Toxicol & Appl Pharmacol 184: 77-81.

R 22

Sarin +PB leads to altered cerebral perfusion

Conclusion: moderate dose sarin + PB for 3 weeks led to significant increase in regional cerebral blood flow in many brain regions -- retained at 2 weeks after d/c treatment, less at 4 weeks

Effect was greater with PB+sarin than sarin alone.

Sarin 0.5LD50 sc 3x/week; PB 80mg/L in drinking water

- Need to look at low level; longterm effect; basal/challenge

Scremin OU et al 2002. Soc for Neuroscience.

R 23

Pesticide Enhances Brain Transit of Subsequent

Conclusion: Very low dose pesticide*

-- equivalent to the amount from eating one apple --

lead to 25-30% increase in subsequent OP in brain (DFP).

*parathion or permethrin but not PB

Vogel JS et al 2002. Protein binding of isoflurophate in vivo after coexposure to multiple chemicals. Environmental Health Perspectives 110 (suppl 8).

R 24

Pesticide Enhances Brain Transit of Subsequent

Subjects: 7-9 week old CD2/F1 male mice

Exposure 1: 1µg/kg parathion (PTN); permethrin (PER) through 5 day cycle

Exposure 2: DFP 1µg/kg

Outcome: Radiolabeled DFP in brain by accelerator mass spectrometry

Result: ~30% increase brain penetration of DFP after very low dose prior exposure to PTN or PER or both.

Vogel JS et al 2002. Protein binding of isoflurophate in vivo after coexposure to multiple chemicals. Env. Health Perspectives 110 (suppl 8).

R 25

Pesticide Enhances Brain Transit of Subsequent

Comment: oral dosing did not lead to markedly less *brain* levels than intraperitoneal dosing, though levels were lower in other tissues.

Vogel JS et al 2002. Protein binding of isoflurophate in vivo after coexposure to multiple chemicals. Env. Health Perspectives 110 (suppl 8).

R 26

I. Summary

This adds to the body of evidence that:
AChE at low levels can, by themselves cause long-term changes in
- ACh neurochemistry,
- Cognitive function, as well as other effects

Effects are exaggerated when chemicals are given in certain settings:

- With other chemicals

- With heat or exercise

Additionally, there are other changes that occur at least in the short term:
- BBB disruption
- Immune system changes
- Cerebral blood flow (higher dose)

R 27

II. Characterizing Problems in III PGW Veterans

R 28

PTSD & CFS-like Illness Increased in PGW Veterans

PGWV have increased rates of CFS & PTSD

CFS patients have altered cholinergic responsivity

PGWV have altered cerebral blood flow

(AChEi cause altered cerebral blood flow)

Muscle symptoms in PGWV are not associated with abnormal EMG/NCV

R 29

PTSD & CFS-like Illness Increased in PGW Veterans

Conclusion: PGW veterans reported significantly higher rates of PTSD and CFS relative to veteran controls.

CONDITION	ADJUSTED OR
PTSD:	3.1 (2.7-3.4)
C FS-like:	4.8 (3.9-5.9)

Kang HK et al 2003. Post-traumatic stress disorder and chronic fatigue syndrome-like illness among Gulf War vetrans: A population-based survey of 30,000 veterans. Am J Epi: 157: 141-148.

R 30

PTSD & CFS-like Illness Increased in PGW Veterans

Subjects:Population-based sample of 15,000 PGW veterans vs 15,000 non-Gulf veterans. Veterans from 4 military branches & 3 unit components (active, Reserve (R), National Guard (NG)). 70% response

Design: Mailed 16 page questionnaire, then phone nonrespondents

Stressor severity: ranked by unit, deployment, combat exposure

Outcome: 1. CDC CFS case def; 2. PTSD Checklist

Result: Incr in CFS than PTSD, crude & adjusted

PTSD: adj OR 3.1 (2.7-3.4)

C FS-like: 4.8 (3.9-5.9)

(Similar OR with and without adjustments.)

Kang HK et al 2003. Post-traumatic stress disorder and chronic fatigue syndrome-like illness among Gulf War vetrans: A population-based survey of 30,000 veterans. Am J Epi: 157: 141-148.

R 31

CFS: enhanced sensitivity of peripheral cholinergic vascular response

CONCLUSION: At all tested doses, 22 CFS patients had increased vascular response to acetylcholine compared to matched controls, on blinded testing. (Vascular response to nitroprusside was not affected.)

- This may provide a useful objective marker for future studies.

- Consistent with our perception, and that of our Expert Panelists, that it may be fruitful to examine markers of ACh function, on challenge testing.

Vance E et al 2000. Am J Med 108 (9): 695-782.

R 32

Details: CFS & cholinergic vascular response

Subjects:22 subjects "randomly selected" from a 420 member local CFS/myalgic encephalitis self-help group, who fulfilled CDC criteria: all with principal complaint of fatigue for >6 mo, mean duration 8±5 yrs. Age 45±9 (26-59). 7 men, 15 women. 22 age and sex matchend controls.

Intervention:

1. Ach iontophoresis: Electrode on forearm provides direct current 0.1mA with 1% ACh chloride for 10 sec to achieve dose of 1mC/cm2. Duration increased to 20, 40, 80sec for 2, 4, 8mC/cm2.

2. Nitropruside iontophoresis

Outcome: Scans for skin erythrocyte flux for 2 min between doses.

Result: Significant increase vascular response to acetylcholine, for all 4 doses, in patients with CFS. No difference in response to nitroprusside.

Vance E et al 2000. Am J Med 108 (9): 695-782.

R 33

PGWV have altered RCBF

35% Higher baseline middle cerebral artery blood flow velocity in symptomatic vs asymptomatic PGW veterans.

Significantly lesser task-associated increase in cerebral blood flow velocity

Also, lower performance on cognitive tests

N = 8 in each group

Bunegin L et al 2001. Toxicol Ind Health 17(4) 128-34.

R 34

PGWV: Defining Physiological Basis of Muscle Symptoms

Conclusion: "Gulf War-related neuromuscular symptoms are not associated with specific impairments of peripheral nerves, neuromuscular junctions, or skeletal muscles":

"our results do not exclude the possibility that some neuromuscular symptoms …may be caused by chemically induced mitochondrial deletions…"

Sharief, Priddin, Delamont, Unwin, Rose, David, Wessely 2002. Neurophysiological analysis of neuromuscular symptoms in Gulf War veterans. Neurology 59: 1518-25.

R 35

Neuromuscular Symptoms: Details

Subjects:142 UK military men (49 Gulf war ill; 26 Gulf War well; 13 Bosnia ill; 22 Era symptomatic) selected from 8195 personnel who had completed other health outcome questions (3531 Gulf War & controls who in database were stratified for age and rank - but not in this sample)

N's small for indiv clinical conditions (e.g. 3 bulbar weakness, 10 fatigue in ill GWV; 4 with lower limb painful sensations)

Nerve conduction: distal motor latency; amplitude of compound motor AP; motor NCV; F-wave latency; sensory AP amplitude (SNAP), peak latency, and CV.

Thermal thresholds. Thermoregulatory fcn of sympathetic skin response through transepidermal water loss.

EMG: prox & distal muscles, upper & lower limbs.

Results: No diff. Few in any symptomatic group had abnormal results.

BUT: 11 of 25 (or 28) with numbness/paresthesia vs 3 of 82 (or 84) without, had abnormal median or ulnar NCV studies -- I.e. the group that "should" have NCV abnormalities

Sharief, Priddin, Delamont, Unwin, Rose, David, Wessely 2002. Neurophysiological analysis of neuromuscular symptoms in Gulf War veterans. Neurology 59: 1518-25.

R 36

II. Review: Findings in PGW Veterans

GWV have CFS (& PTSD)

CFS patients (not separately evaluating GWV) have altered cholinergic vascular responsivity

PGW veterans may have altered cerebral autoregulation

The character of muscle findings is not of the type that is detected by EMG/NCV (though peripheral neuropathy may be)

R 37

III. Symptoms in OP Pesticide Exposed Persons -- Another setting with AChEi Exposure

R 38

Postal Survey: Increased Symptoms in Farmers Exposed to OPs

Postal Survey #1:

Significantly increased symptoms in OP exposed vs non-exposed farmers: p < 0.0001 greater # symptoms in OP-exposed group.

Symptoms relevant to ill PGW veterans: cognitive, fatigue, weakness, mood, smell sensitivity

Postal Survey #2:

Symptom patterns essentially identical whether sheep dip vs exposed to OPs in other ways.

Davies 1999. J Nutr Env Med. 9: 123-34.

R 39

Davies, Postal Surveys, Cont'd

Subjects, #1: 400 farmers names randomly selected from Yellow pages for Cornwall and West Devon. 179 returned (44.6% response).

N=45 non-OP exposed; n=135 OP-exposed. 3 dead, 1 unusable

OP Exposure 1: Brief questionnaire: direct questions about OP exposure over the 10 yrs prior to receiving questionnaire

Outcomes: Yes/No questions re: sx of COPIDN.

Sx include those directly relevant to ill pGWV: memory/concentration; sensitivity to smells & chemicals; weakness & fatiguability; mood/irritability. (Questionnaire included.)

Result:

87% of nonexposed reported 0 sx, vs 41% of exposed.

25% of exposed reported 5-8 sx vs 0% of unexposed.

41% vs 4% reported ≥3 sx.

p < 0.0001 greater # symptoms in OP-exposed groups

R 40

Davies, Postal Surveys, Cont'd

Subjects, #2: OP information network provided 240 names of persons who had registered their concerns. 90% response rate.

OP Exposure 2: by questionnaire

Result#2: pattern of sx similar between sheep dippers and those exposed in other ways. Also similar btn study 1 and study 2

e.g: >90% both groups report:

- cognitive problems
- decreased exercise tolerance (fatiguability/ strength)
- personality change.

>80% report OP sensitive status (both groups for study 1 and the study 2 group)

R 41

Behavioral Effects of OP exposure in Greenhouse Workers

Conclusion: Compared to unexposed women, women with OP exposure had fatigue, cognitive/mood, and motor problems - some objective tests and some subjective tests.

(Findings included: Increased fatigue; longer reaction times; greater depression and tension, reduced motor steadiness; and more frequent symptoms related to fatigue, weakness, cognition, irritability, sleep, sweats, GI dysfunction, headaches, and smell sensitivity.)

Bazylewicz-Walczak et al. Neurotoxicology 1999: 20(5):819-26

R 42

Behavioral Effects of OP exposure in Greenhouse Workers

Subjects: 26 women occupationally exposed to several OPs in greenhouse planting jobs; 25 women in gardening enterprises not exposed to neurotoxic chemicals, similar in age, education, place of habitation, and intake of stimulants and drugs

Exposure: determined in planting period. Total exposure in the exposed group was low.

Outcomes: Psychological eval performed before and after spraying season. Neurobehavioral Core Battery Test, recommended by WHO, to all. NOTE: not different before vs after spraying season (long-term effect).

Bazylewicz-Walczak et al. Neurotoxicology 1999: 20(5):819-26

R 43

Polish Greenhouse Workers, cont'd

Polish adaptation of Neurobehavioral Test Battery, recommended by WHO. Includes:

- Simple Reaction time
- Digit Symbol
- Digit Span
- Benton Visual Retention (recognition form)
- Santa Ana
- Aiming
- Profile of Mood States
- Finnish Subjective Symptoms Questionnaire (included in paper -- includes fatigue, weakness, sleep, memory, concentration, irritability, headaches, sweats, diarrhea/constipation, paresthesias, smell, taste, tremor, walking in the dark)

Bazylewicz-Walczak et al. Neurotoxicology 1999: 20(5):819-26

R 44

NHIS Mortality Follow-up: Incr Accidental Death in Pesticide Exposed

Conclusion: Compared to all other workers, farmers and pesticide applicators -- those with presumed pesticide exposure -- were at increased risk for accidental mortality.

Also at increased risk for hematopoietic and nervous system cancers.

Fleming LE et al 2002. Am J Ind Med 43: 227-233

R 45

NHIS Mortality Follow-up: Incr Accidental Death in Pesticide Exposed

Subjects: 9471 farmers and pesticide applicators with 571 deaths, compared to 438,228 other US workers with 11,992 deaths, 1986-1994 National Health Interview Survey (NHIS) data

Outcome: Age adjusted risk of accidental death; and also of specific cancers

Analysis: Cox regression (survival analysis)

Fleming LE et al 2002. Am J Ind Med 43: 227-233

R 46

NHIS Mortality Follow-up: Incr Accidental Death in Pesticide Exposed

Age Adjusted

Cause of death	Male RR	Female RR
All	1.2 (1.1-1.3)	1.1 (0.8-1.4)
MVA/accidents	1.6 (1.2-2.2)	3.2 (1.5-6.9)
Overall cancer	1.2 (1.0-1.4)	1.0 (0.7-1.5)
NS cancer	2.1 (1.0-4.5)	2.4 (0.6-8.8)
Lymphatic/bld	3.6 (1.6-8.2)	2.2 (1.5-3.2)

Note: comment on healthy worker effect

Fleming LE et al 2002. Am J Ind Med 43: 227-233

R 47

ACh-drugs for treatment?

Choline

Muscarinic

Nicotinic

Downstream agents (GABA-ergic)

R 48

Choline

Choline: precursor to acetylcholine

Choline has direct alpha-7 nicotinic AChR binding

Choline and other alpha-7 agonists offers cytoprotection (protection against cytotoxicity) in a variety of experimental models in which cytotoxicity is experimentally induced.

Jonnala RR et al, Synapse 2003 47(4):262-9

R 49

Nicotinic Agonists: Nicotine

Nicotine has neuroprotective effects, possibly because it upregulates alpha-7 nicotinic receptors.

Terry AV et al 2002. J Pharmacol Exp Ther 2002. 301(1):284-92

R 50

Nicotinic Agonists: Nicotine

- Nicotine pretreatment reduces cell death caused by cytotoxic environment (deprive cells of NGF and serum).

- Protection is blocked if give selective alpha-7 blocker MLA (methyllycaconite).

- Other tested nicotinic agonists also are protective, though less so than nicotine. The next most protective group among agonists tried included epibatidine, 4OHGTS-21, methycarbamylcholine, and 1,1-dimethyl-4-phenyl-piperazinium iodide.

- The most protective ones increased labeled alphabungarotoxin binding sites the most - also suggesting again that upregulation of alpha-7 may be the mechanism

Terry AV et al 2002. J Pharmacol Exp Ther 2002. 301(1):284-92

R 51

Nicotinic Agonists: Nicotine

Nicotine: improves attention and reduces distractibility in humans (literature in dementia and normals)

Nicotine normalized persistent deficits in memory function in rats previously exposed to repeated low level DFP.

Stone JD et al 2000. Brain Res 882 (1-2): 9-18.

R 52

Nicotinic Agonists: Nicotine

Nicotinic agents administered systemically have pain-relieving effects if there is nerve injury.

a4b2 subtype of nicotinic receptor was responsible, with nicotine; a different receptor with epibatidine.

Muscimol, a GABA agonist, also has this effect; and GABA blockers had opposite effect, suggesting the ACh-GABA system is responsible.

*Paw pressure test: reduces pain in animals with nerve injury but not normal animals.

Rashid Md. & Ueda H 2002. Brain Res 953: 53-62.

R 53

Nicotinic Agonists

SIB-1553A = an agonist of the human beta-4 nicotinic receptor: improved attention and reduced distractibility in rats with impairments in these areas (but not in normal rats).

*Impairment was produced by the NMDA antagonist dizocilpine

Terry AV et al 2002. J Pharmacol Exp Ther 2002. 301(1):284-92

R 54

Muscarinic M-1 Agonists

Talsaclidine: improve performance on a memory test* in rhesus monkeys, by 7-10%.

WAY 132983: improved performance on a memory test* in rhesus monkeys by 16%.

Comment: Different doses were optimal for different animals.

*Delayed match to sample

Terry AV et al 2002. Psychopharmacology (Berl) 162(3):292-300

R 55

ACH Agents

In animals: ACh agonists lead to:

- Improved cognitive function
- Pain relief
- Fatigue & weakness (reviewed previously)
- Protection of cells from ongoing injury

R 56

Summary

Low level AChEi leads to persistent and delayed adverse effects to the nervous system and other elements of physiology. These effects include altered regulation of the ACh system. Exercise, stress, heat, and other chemicals can exaggerate or enable some of these effects. Some effects may respond to ACh agonists.

Gulf War veterans problems continue to be defined; work defining altered cholinergic mechanisms, and other mechanisms holds promise

Persons with AChEi exposure in other settings appear to have a similar constellation of persistent symptoms - & similar predisposition (PON)

Work on AChE agonists provides one potentially fruitful line of approach: these benefit cognition, pain, fatigue, muscle fcn in animal studies and studies in humans.

Appendix F

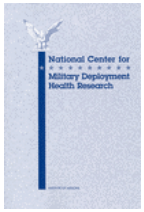
"A New Era of Caring for Combat Veterans: Clinical & Research Activities of the War-Related Illness and Injury Study Center"

February 3, 2003

Washington, D.C.

Genesis - Legislation

- **Public Law 105-368: The Veterans Program Enhancement Act of 1998, Sec. 103**
- **National Center on War-Related Illnesses and Postdeployment Health Issues**
- **NAS/IOM Committee on a National Center on War-Related Illnesses and Postdeployment Health Issues, November 1999**
  - **9 member committee chaired by M Greenlick, MD, endorsed a VA plan similar in structure to GRECC**



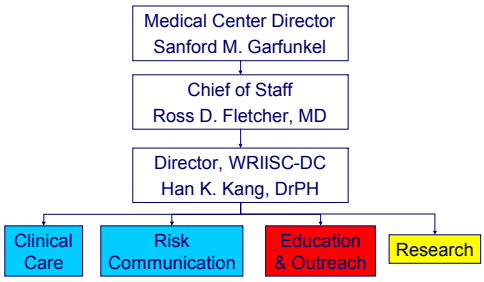
Genesis - Timeline

Aug 24, 2000	**Request for Proposals for New Centers for the Study of War-Related Illnesses**
Oct 1, 2000	**Letter of Intent submitted**
Dec 1, 2000	**Proposal submitted**
Apr 1, 2001	**Site Visit at Washington, DC VAMC**
May 10, 2001	**Selection of Washington, DC & East Orange, NJ VAMCs**

Mission Statement

To improve the health of combat veterans through clinical care, risk communication, education, and research addressing deployment related exposures and the risk of latent illness, injury and disability.

WRIISC-DC Organization



WRIISC-DC Conceptual Model

WRIISC-DC Staff Directory

Han Kang, DrPH	Director
Mitchell Wallin, MD, MPH	Clinical Director
Mian Li, MD, PhD	Co-Clinical Director
Michelle Prisco, ANP-C, MSN	Research Nurse Practitioner
Andrew Lincoln, ScD, MS	Education Director
Aaron Schneiderman, RN, PhD	Risk Communication Director
Clare Mahan, PhD	Statistician
Tim Bullman, MS	Data Manager
Marina Dobrovitsky, MA	Research Analyst
Patrick Miller, BA	Health Education Intern
Antoinette Workeman	Administrative Officer

Collaborators

- **George Washington University**
  Paul H. Levine, M.D.; Samuel J. Simmens, Ph.D.
- **Johns Hopkins University**
  Barbara Curbow, Ph.D.; Genevieve M. Matanoski, M.D., Dr. P.H.; Peter St. John Lees, Ph.D.
- **Department of Defense**
  Center for Health Promotion and Preventive Medicine (CHPPM):
  Jack M. Heller, Ph.D.; Mark Rubertone, M.D., M.P.H.
  Walter Reed Army Medical Center (WRAMC):
  Charles C. Engel, M.D., M.P.H.; David N. Cowan, Ph.D.
  Uniformed Services University of the Health Sciences (USUHS):
  David H. Trump, M.D., M.P.H.; Gary Gackstetter, DMV, Ph.D.

Summary

Eight FTEEs

$1.1M Core Funding per Year

Serves as one of the two inpatient referral centers for war-related illnesses & injuries

Funding renewal after 3 years

To create a "center of excellence" for research, education, risk communication and clinical care in deployment-related illness and injury

Clinical Care Objectives

- Develop innovative clinical strategies for war-related illnesses
- Develop effective education techniques for the clinical setting
- Implement clinical algorithms into primary care settings for evaluation of veterans with war-related illnesses

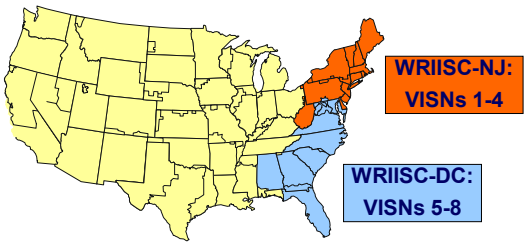
Clinical Care Program

- Referral source for veterans with war-related health concerns and difficult to diagnose war-related illnesses and injuries
- Examine, manage, and provide consultation services to veterans with war-related illnesses and injuries
- Two major clinical care programs
  - WRIISC National Referral Program
  - WRIISC Outpatient Clinic

National Referral Program

- Designed for veterans with difficult to diagnose war-related illnesses and injuries outside driving distance to Washington, DC
- The program serves as a focused second opinion evaluation for veterans with war-related concerns

Distribution of WRIISC Referrals

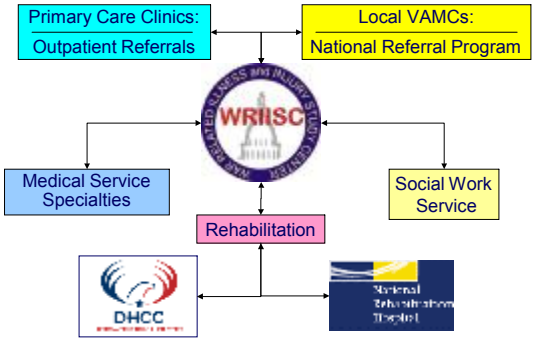


Referrals from remaining VISNs are alternated between the WRIISCs

WRIISC Outpatient Clinic

- Specialty clinic for outpatient referrals with war-related concerns, illnesses, or injuries.
- Initial evaluation will serve to direct further care within VAMC or collaborative clinics.
- Clinic will help coordinate specialty referrals and ultimately refer the veteran back to his/her primary medical provider for follow-up.

Clinical Program Interface



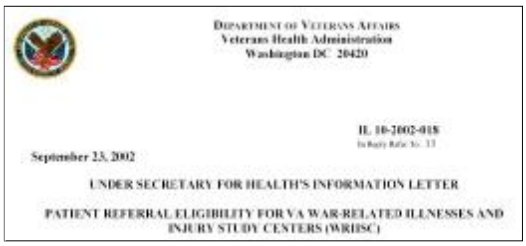
Clinical Resources

- EEG/EMG Lab
- Sleep Lab and EEG Monitoring Beds
- Neuropsychology Lab
- Magnetic Stimulation Lab
- Multidisciplinary Pain Treatment Program
- MRI
- NRH Specialty Clinic
- WRAMC Deployment Health Clinical Center
- Specialty Consultative Services

Clinical Status Report

- Weekly outpatient clinic initiated in April 2002— 80 veterans evaluated
- Inpatient WRIISC referral program initiated in Jan 02—16 completed
- Implementing DoD-VA Clinical Practice Guideline on Post-Deployment Health Evaluation & Management within primary care environment

Eligibility



DEPARTMENT OF VETERANS AFFAIRS
Veterans Health Administration
Washington DC 20420

IL 10-2002-018

September 23, 2002

UNDER SECRETARY FOR HEALTH'S INFORMATION LETTER

PATIENT REFERRAL ELIGIBILITY FOR VA WAR-RELATED ILLNESSES AND INJURY STUDY CENTERS (WRIISC)

Eligibility

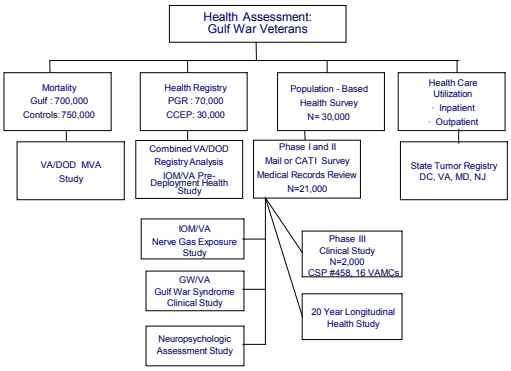
- New VHA patients must first contact the VAMC Eligibility Office
- All eligible veterans are assigned to a primary care provider, who may refer the veteran to the WRIISC Clinic
- "Combat Service Veteran" as defined by DoD
- Have unexplained symptoms felt to be associated with combat service or other deployment-related experience
- Medically and psychiatrically stable for travel
- Willing to participate in evaluation and treatment recommendations

Research Program Objective

To investigate the health consequences of deployment in a combat theater with a specific focus on deployment-related exposures and the risk of latent illness, injury, and disability.

Research Interests

- Health consequences of war
- Post service cause-specific mortality from diseases and injuries
- New or unusual infections
- Chronic medical and psychological conditions
- Adverse reproductive health outcomes
- Disability resulting from deployment illness or injury
- Health care utilization



Results: Mortality Studies

1. Overall mortality rate of Gulf War veterans is not higher than non-Gulf veterans.
2. Mortality rates from injuries, especially motor vehicle crashes, were higher among Gulf War veterans than non-Gulf veterans
3. Mortality rates for disease-related cases were lower among Gulf War veterans than non-Gulf veterans.
4. These differences in mortality patterns began to dissipate 5 years after the war.
5. Both Gulf and non-Gulf veterans mortality rates remained less than half that expected from their civilian counterparts.
6. Both US and UK study results are remarkably similar

Ref: NEJM,1996;335:1498; Am J Epi,1998;149:324; Am J Epi, 2001;154:399 Occup Environ Med, 2002;59:794

Health Care Utilization Findings

1. No excess postwar hospitalization (1991-1994) due to major categories of diseases in VA, DoD and California hospital systems
2. A small, yet significant, excess in hospitalization was observed among Gulf veterans due to mental disorders, diseases of respiratory system and the digestive system, diseases of skin, and other symptoms, signs and ill-defined conditions

Ref: NEJM,1996;335:1498; Am J Epi,2000;151:63

National Health Survey Findings: Phase I and II

I. Physical Health

Gulf veterans reported higher prevalence of

- A wide variety of symptoms
- Health care utilization
- Serious chronic health conditions
- Lower perception of general health
- Functional impairment

Ref: J Occup Environ Med 2000;42:491

National Health Survey Findings: Phase I and II

II. Psychological Health

- Gulf veterans reported higher prevalence of symptoms endorsing PTSD (PCL-M) and chronic fatigue syndrome (CDC 1994)
- The prevalence of PTSD increased monotonically across 6 levels of deployment-related stress intensity (test of trend, p <0.01)
- Gulf veterans reported higher rate of sexual trauma (harassment/assault) in theater, which in turn was associated with the higher prevalence of PTSD even after adjusting for the combat trauma.

• Ref: Am J Epi,2003;157:141-148

National Health Survey Findings: Phase I and II

III. Reproductive Health

Gulf veterans reported higher rates of:

- Miscarriage
  - Male veterans: OR=1.62; 95% CI=1.32-1.99
  - Female veterans: OR = 1.35; 95% CI =0.97-1.89
- Birth defects among liveborn infants
  - Male veterans: OR = 1.78; 95% CI=1.19-2.66
  - Female veterans: OR= 2.80; 95% CI=1.26-6.25

Ref: Ann Epi,2001;11:504

National Health Survey Findings: Phase I and II

IV. Symptom Cluster

- A cluster of symptoms consistent with neurological impairment: blurred vision, loss of balance/dizziness, tremors/shaking and speech difficulty
- The symptom complex appears to correlate with objective neurological abnormalities including abnormal ENG
- Relatively more symptomatic Gulf veterans were exposed to combat, engaged in military duties in Kuwait and Iraq, and potential nerve gas plume from Khamisiyah incident as determined by the Department of Defense

Ref: Arch Environ Health,2002;57:61

Current Studies

- Study of Fatal Motor Vehicle Crashes of Gulf War and Non-deployed Veterans
- Mortality and Morbidity Among U.S. Gulf Veterans Who Were Potentially Exposed to Nerve Gas at Khamisiyah, Iraq
- Study of Health Outcomes & Environmental Surveillance (SHOES) in Bosnia/Kosovo
- Longitudinal Health Study of Gulf War Era Vets

Study of Health Outcomes & Environmental Surveillance (SHOES) in Bosnia/Kosovo

- Collaborators:
  - Army Medical Surveillance Activity
  - Deployment Environmental Surveillance Program
- Specific Aims:
  - To develop a model data repository linking military service records and VA records
  - To combine advancements in exposure assessment with health and illness experience to investigate the effects of deployment of armed forces personnel
  - To explore topical research questions and validate findings of other veteran cohorts

Study of Health Outcomes & Environmental Surveillance (SHOES) in Bosnia/Kosovo

- Application of SHOES
  - Is there an excess mortality from MVC among B/K veterans as with other veteran cohorts?
  - How were environmental exposures correlated with short & long-term health outcomes?
  - How do environmental monitoring data correlate with biomarker data?

Longitudinal Health Study of Gulf War Era Vets

- PIs: Han Kang, DrPH; Seth Eisen, M.D., St. Louis VAMC; Charles Engel Jr., M.D., WRAMC
- Study Design:
  - Longitudinal study of a permanent panel of 15,000 Gulf veterans and an equal number of non-Gulf veterans identified for the National Health Survey.
- Specific Aims:
  - To determine the health status of Gulf War veterans relative to non-Gulf War veterans ten or more years after the war.
  - To characterize how the health status of Gulf War and non-Gulf War veterans has changed in the past 5 years.
  - To compare the current health of Gulf War veterans with civilian peers.
  - To assess the role of complementary and alternative medicine in the health of Gulf War veterans

Questions?

Appendix G

New Jersey WRIISC

- Director: Benjamin Natelson MD
- Associate Directors
  - Clinical: Drew Helmer MD MS
  - Education: Liesel Copeland PhD
  - Risk Communication: Susan Santos PhD
  - Research: Thomas Findley MD PhD

Clinical Paradigm

- We are a consultation service.
- We evaluate the medical records for missed diagnoses or inadequately treated conditions.
- We evaluate the veteran personally for new diagnoses.
- We fully discuss all deployment-related health concerns with the patient.
- We perform the necessary tests to confirm or refute a diagnostic possibility (with limits).
- We make recommendations for treatment and/or further work up for the patient and his or her health care provider to implement at home.

Standard Features

- History & physical
- Psychological assessment
- Risk communication interview
- Fitness testing
- Sensory testing
- Balance testing
- Education session

WRIISC Education Goals

1. Provide education and educational resources about unexplained illnesses to veterans and providers
2. Support Clinical Program and Risk Communication activities
3. Conduct educational research to improve access or use of education and resources

Education Activities

- Publish feature articles in *Veterans' Advantage* magazine
- Distribute Center's informational fact sheet to veterans' organizations
- Active website **www.wri.med.va.gov** receives an average of 80 "hits" per day
- Fact Sheet for patients on medically unexplained illness and on benefits of exercise
- Submit project proposal on testing delivery methods of health education to soldiers being deployed at Fort Dix, NJ
- Monthly seminar series for health care professionals

Risk Communication Activities

- Continued Support to Clinical Program
  - -Initial and Exit Interviews
  - -Patient "friendly" Summaries
- Support to Education
  - **Material for Website**
  - **Medical Grand Rounds Presentation on Risk Communication and Unexplained Illness**

Risk Communication Activities

- Developed new instrument to explore how Veterans "think about" Deployment Related Exposures (risks of exposure, symptoms vs disease, health care management, etc)
- Instrument also explores how Veterans perceive "stress" and relationship to health outcomes

Research Activities

- Research Areas
  - Physiology of Unexplained Illness
  - Health Services and Systems
  - Perception of Symptoms
  - Research Training
- Funding
  - Only 2 pilots funded with WRIISC

Research Grants Funded/Pending

- Physiology of unexplained illness (29)
  - Stress(5), pain(3), sleep(4), balance(2)
  - Neurophysiology(9), FM/CFS (6)
- Health services and systems (13)
  - LVHS large data base(8), providers(2)
  - Utilization (3)
- Perception of symptoms (12)
  - Symptoms(8) Risk communication(4)
- Research training (4)

Benjamin H. Natelson, MD

- Areas of Expertise: Medically unexplained illnesses, behavioral medicine, adrenal axis
- Funded: NIH CFS CRC, VA MR
  - Physiology and natural history of CFS
  - Adrenal function in Gulf Vets with CFS
- Pending: NIH RO1s (Sleep and Cytokines in CFS and FM); HSRD, VA Communications about Bioterrorist Attacks

Thomas W. Findley MD, PhD

- Areas of Expertise: Physiatry; disability and functional assessment; mathematical modeling
- Funded: HSR&D IIR
- Pending: HSR&D REAP
- Pilots: Balance Deficits
- 3/15 Health Services Rehabilitation Research Center (approved LOI)
- 4/15 VA Rehab: Mathematical modeling of balance to evaluate interventions (approved LOI)

Susan L. Santos, MS, PhD

- Areas of Expertise: Risk Communication and Risk Perception of Deployment Related Health Risks, Differences in Perceptions of VA Physicians/Veterans about Medically Unexplained Illness, Communicating Risks and Benefits of Preventative Measures, Environmental Risk Communication
- Funded: NEIHS grant (with Boston University)
- Pilot: Risk Perception of Veterans with MUS
- Pending: VA HSRD Bioterrorism; DOD Deployment Related Message Development; US EPA NCER Comparative Use of Three Evaluative Tools to Empower Communities in the Cleanup of Sediment Contaminated Sites

Liesel Copeland, PhD

- Areas of Expertise: Educational & survey research, web-based education and program evaluation
- Funding: VA VISN
  - Templates for drug ordering and evaluation of their utility
- Pending: DOD
  - Evaluating different methods for predeployment education/risk communication about stress and unexplained illnesses

Drew Helmer, MD

- Areas of Expertise: Internal medicine, ambulatory care utilization, risk communication
- Pending: VA HSRD
  - Bioterrorism and communication in the VA
  - Preventable hospitalizations in diabetes
- Planned: VA HSRD RCD
  - Health care utilization in vets with unexplained symptoms and those with diabetes

John E. Ottenweller, PhD

- Areas of Expertise: Long-term effects of chronic stress, adrenal axis, BuChE and PON
- Funding: VA MR, WRIISC Pilot
  - CNS mechanisms governing persistent stress effects
  - Cortisol, BuChE and PON in Gulf Era Veterans
- Pending: VA Epidemiology
  - Cytokines in Gulf Era Veterans and Spouses

Dane B. Cook, PhD

- Areas of Expertise: Exercise physiology, psychophysics, pain and fMRI
- Funding: WRIISC Pilot
  - Measuring pain sensitivity, exercise-induced analgesia and cytokines in Gulf Vets with pain
- Pending: VA MREP
  - Functional brain imaging (fMRI) of pain in Gulf vets who have unexplained pain

Richard J. Servatius, PhD

- Areas of Expertise: Physiological Psychology, Learning and Behavior, Stress and PB
- Funding: VA MR, NIH
  - CNS effects of combining PB and stress
  - Learning and Memory in CFS

Shelley Weaver, PhD

- Area of Expertise: Adrenal axis and individual differences in responses to stress and toxins
- Pending: VISN 3 SEED and NIH RO3
- PILOTS: Neuronal protein markers of persistent effects of severe stressors
- Proteomic analysis of cerebrospinal fluid in patients with medically unexplained fatigue

Karen Quigley, PhD

- Areas of Expertise: Physiological and psychological factors in stress reactivity
- Funding: CFS CRC Pilot; ONR
  - Balance testing in CFS
  - Cognitive modeling of stress reactivity
- Pending: VA MRS, VA HSRD
  - Risk communication, stress and experimental vaccines
  - Prospective study of stress reactivity and psychosocial factors pre-deployment affect post-deployment health

Roles of BuChE, PON and Stress in Unexplained Illnesses

- Assayed 3,257 samples and sent data to Hines Co-op Studies Center
  - Outstanding Quality Control during Assays
- Dr. Alpern assigned as project statistician
- Planning statistics begun by Conference Call with Executive Committee for Project
- Expect Preliminary Analyses by Feb 2003

Pain Sensitivity in Gulf Veterans with Unexplained Musculoskeletal Pain

- Psychophysical assessment procedure has been tested and found to be reliable
- Luminex cytokine analyzer calibrated and tested
- Five subjects (3 healthy and 2 sick) have been tested, with 10 additional ready to be scheduled
  - Preliminary evidence for hypersensitivity in GVs with unexplained pain
- On schedule for completion of subject testing this summer

Postural Stability: Mathematical Modeling

- Developed 4 link model
- Applied 2 link model to existing data
- Calculated ankle stiffness from balance test
- 17 Vets, 10 CFS, 8 normals tested
- CFS and vets decrease in balance
- Adding position sensors for additional links
- First paper submitted

Prospective Study of Functional Status in Veterans at Risk for Unexplained Illness

- Quigley, Findley, Helmer, Weaver, et al.

- **Aim 1**: To determine if pre-deployment variables like personality traits (e.g., neuroticism), and behavioral and physiological tendencies (e.g., current non-specific symptom reporting, or neuroendocrine reactivity) are associated with poorer post-deployment functional status.

- **Aim II:** To determine if pre-deployment coping style and pre- and immediate post-deployment social support can buffer post-deployment reductions in functional status.

- **Aim III:** To determine whether immediate post-deployment variables like decreased functional status, decreased emotional control, increased psychological distress, and reduced or augmented social support predict later increased health care utilization.

Appendix H

Retrieval of cholinergic balance by antisense oligonucleotides: From animal models to clinical trials

Hermona Soreq
Institute of Life Sciences, The Hebrew University of Jerusalem, Israel

Recently accumulated evidence demonstrates frequent disease-related changes in the alternative splicing patterns of gene products controlling numerous physiological functions[1]. The efficacy of antisense targeting one of the several splicing variants of such mammalian genes was tested for acetylcholinesterase (AChE). The enzyme, AChE, is intimately involved in cholinergic neurotransmission[2]. Alternative splicing induces, under conditions of cholinergic imbalance, overproduction of the rare "readthrough" variant AChE-R mRNA[3]. In mice, this is associated with electrophysiological hyperactivity[4], impaired working memory[5], hypersensitivity to head injury[6], prolonged contextual fear responses[7] and weakened muscles[8]. All of these are transiently alleviated by murine (m)EN101, an antisense oligonucleotide that selectively induces the destruction of mouse AChE-R mRNA[9]. The pathophysiological relevance of AChE-R accumulation to neuromuscular functioning was evident from the accumulation of serum AChE-R in patients with myasthenia gravis (MG) and rats with experimental autoimmune MG (EAMG), both neuromuscular junction diseases with depleted acetylcholine receptors. In EAMG, we alleviated electromyographic abnormalities by nanomolar doses of rat (r)EN101, shown to selectively lower AChE-R in blood and muscle, yet leave unaffected the synaptic variant, AChE-S. While animals treated with placebo or conventional cholinesterase inhibitors continued to deteriorate, a 4-week daily oral administration of rEN101 improved survival, neuromuscular strength and clinical status in moribund EAMG rats[10]. Cynomolgus monkeys maintained normal health and locomotion activity during one week of oral or intravenous administration of human (h)EN101, which reduced AChE-R mRNA levels in spinal cord neurons and suppressed the cholinergic input into motoneurons. Finally, in clinical trials, human MG patient volunteers responded to one week oral hEN101 administration with conspicuous improvement in muscle functioning. These multi-species findings highlight the advantages of mRNA-targeted therapeutics for retrieving normal patterns of alternative splicing and achieving physiological homeostasis.

References

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[2]Soreq and Seidman (2001). Acetylcholinesterase – new roles for an old actor. *Nature Neurosci. Rev*. **2**, 294-302.

[3]Kaufer *et al.* (1998). Acute stress facilitates long-lasting changes in cholinergic gene expression. *Nature* **393**, 373-377.

[4]Meshorer *et al.* (2002). Alternative splicing and neuritic mRNA translocation under long-term neuronal hypersensitivity. *Science,* **295***,* 508-512.

[5]Cohen *et al*. (2002). Overexpression of "readthrough" acetylcholinesterase is associated with antisense suppressible behavioral impairments. *Mol. Psychiat.* **7,** 874-885.

[6] Shohami *et al.* (2000). Antisense prevention of neuronal damages following head injury in mice. *J. Molecular Medicine*, **78**, 228-236.

[7] Birikh *et al*. (2003). Interaction of "Readthrough" acetylcholinesterase with RACK1 and PKCβII correlates with intensified fear induced conflict behavior. *PNAS*, in press.

[8] Farchi *et al*. (2003). Chronic acetylcholinesterase overexpression induces multileveled aberrations in neuromuscular physiology. *J. Physiol.*, in press.

[9] Galyam *et al*., (2001). Complex host cell responses to antisense suppression of ACHE gene expression. *Antisense and Nucleic Acid Drug Development*, **11**, 51-57.

[10]Brenner *et al*. (2003). The role of readthrough acetylcholinesterase in the pathophysiology of myasthenia gravis. *FASEB J*., in press.

Appendix I

Research Advisory Committee on Gulf War Illnesses

Discussion of Treatment Recommendations
Lea Steele, Ph.D.

Overview of Draft Recommendation

- "Umbrella" recommendation that VA establish a program specifically tasked with proactively identifying, developing, and evaluating treatments for Gulf War Illnesses
- Two appendices outline considerations for:
  (A) prioritizing treatments for study
  (B) identifying treatments being used and assessing evidence for their effectiveness
- Additional section/appendix to recommend studies of specific treatments?

Background: Federal Imperative to Identify Treatments for Gulf War Illnesses

- Congress, Federal PGW Coordinating Board, VA have designated identification of treatments for GWI to be a top priority
- VA has maintained open solicitation for GWI treatment trials since 1997
- Few treatments studied: 2 large multicenter RCTs (ABT, EBT)
- IOM panel recommended using "hierarchy of evidence" approach to treatment research
- Virtually no progress in achieving this goal

Background: Treatment Research at VA

- VA-sponsored research studies are almost always investigator-initiated
- No mechanism for proactively identifying treatments, or developing evidence in support of candidate treatments for trials
- No evaluation of outcomes associated with treatments used or recommended for unexplained illnesses in Gulf veterans
- Success in finding treatments is unlikely without a new approach

Background: Treatment Research at VA

- <u>Success in finding treatments is unlikely without a new approach</u>
  - Current approach hasn't produced results
  - GWI difficult to study, difficult to treat
    Sufficient interest, expertise in treating unexplained illness among VA clinicians?

Recommendation

Establish a comprehensive program to proactively identify, develop, and evaluate treatments for Gulf War illnesses

- Staffed by professionals with appropriate expertise
- New program would be in addition to current VA research programs
- Additional new initiatives provide a framework for evidence-based identification and development of treatments

-

New Recommended Program Initiatives:

- Identify treatments currently being used
- Determine outcomes associated with current treatments, VA-recommended treatments
- Plan for developing and testing untried treatments
- Protocol for assessing evidence re: treatments, determining next step
- Technical assistance to clinicians for developing datare: treatment effectiveness
- Establish guidelines, standards for GWI treatment research

Appendix A: Considerations for Prioritizing Candidate Treatments for Trials

- Evidence of effectiveness
- Safety
- Range of symptoms expected to benefit from treatment
- Strength of biological rationale
- Widely used?
- Difficulty and cost of evaluation

Appendix B: Considerations for Identifying and Evaluating Treatments That Have Been Used to Treat Unexplained Illness

- <u>Identify treatments currently being used within and outside VA</u>
  - Existing VA clinical records
  - Survey veterans, clinicians
- <u>Assess effectiveness of treatments currently being used</u>
  - Existing clinical records
  - Follow-up with veterans treated at PGW clinics
  - Establish outcomes monitoring programs
  - Experience of other agencies in developing protocols for evaluating unstudied treatments in clinical practice
- <u>Develop additional data when indicated</u>
  - Evaluate evidence re: treatment, determine appropriate next step
  - Technical assistance for clinicians to collect interpretable data
  - Review panel to prioritize and advise next steps re: treatment evidence

Experience of Other Agencies re: Evaluation of Unstudied Treatments in Clinical Practice

- Usual drug development model depends on extensive "preclinical" data
- This is not available for Gulf War illnesses
- 1990: OTA proposed a mechanism to evaluate novel cancer therapies in medical practices to identify preliminary evidence of disease improvement

  - NCI: "Best Case Series" program for evaluating novel cancer therapies
  - NCCAM: "Prospective Outcomes Evaluation and Monitoring"
  - CDC: Adaptation of Epi Field Methods to clinical practice evaluation

Experience of Other Agencies re: Evaluation of Unstudied Treatments in Clinical Practice
<u>Lessons Learned</u>

- ✓ Requires clear documentation of disease, treatment, and health outcome
- ✓ Routine clinical data is often not adequately informative
- ✓ Technical assistance needed for clinicians
- ✓ Outside review panel useful in prioritizing, recommending next steps

Recommendation

RAC recommends that VA establish a comprehensive program to proactively identify, develop, and evaluate treatments for Gulf War illnesses.

Appendix A: Considerations for Prioritizing Candidate Treatments for Trials

Appendix B: Considerations for Identifying and Evaluating Treatments That Have Been Used to Treat Unexplained Illness

Should RAC Recommend that VA Study Specific Treatments that Have Not Yet Been Tried on ill Veterans?

- Preliminary list
  - Treatments affecting acetylcholine dysregulation
    - Israeli antisense myasthenia gravis drug (inhibits AChE)
    - Other
  - Treatments that may benefit mitochondrial function
    - CoQ10
    - Other
  - Treatments that enhance oxygen delivery
    - Hyperbaric oxygen
    - Other
  - Treatments used in CFS, MCS, FMS
    - Sauna detoxification therapy
    - Other

Should We Recommend that VA Study Specific Treatments that Have Not Yet Been Tried on ill Veterans?

- Pros
  - Good hypotheses, should be pursued
  - Unlikely that these treatments will be studied without specific recommendation
  - Would serve as examples of general approaches worth considering
  - Convey to veterans, VA, researchers that committee has reviewed and considered specific treatments

Should We Recommend that VA Study Specific Treatments that Have Not Yet Been Tried on ill Veterans?

- Cons
  - Based on speculation; most associated with no clinical experience for GWI or similar conditions
  - In some cases, rationale for use also speculative
  - Can a government agency administer a therapy for which there is no preliminary indication of effectiveness?
  - Should they?

Appendix J

Research Recommendations:
Ideas for Discussion

R 1

Draft Research Recommendations: Focus on AChEi

- Genetic & Pharmacological Animal Models
- Objective Markers
- Studies of Other AChE Exposed Groups
- Treatment Trials
- Brain Banks
- Genomic & Proteomic Screens

R 2

Genetic & Pharmacological Animal Models

Advantages:

- Help to define mechanisms
- Help to identify objective markers
- Provide means for developing treatments
- Already leading to critical insights & promising ideas re: treatments

"What's not to like"

R 3

Objective Markers

A) Identify objective markers that result following AChEi exposure, pertaining to 1) changes in ACh system function; 2) altered biology distinct from ACh system function (e.g. membrane effects, oxidative injury, cytokine changes, mitochondrial effects).

B) Identify objective markers not associated with AChEi, for case definition (e.g. squalene antibodies).

Advantages:

- Help to define causes:Identify in animals which exposures/combinations produce the relevant objective marker
- Permit translation between animal & human studies
- Define targets for treatment
- Define illness subsets
  - permit targeted study of disease (natural history, prognosis)
  - Treatment trials can be targeted to those in whom benefit might be seen (enhance power, reduce cost, reduce morbidity)
  - Tested treatments can be targeted to those who may benefit

R 4

Study Others with AChEi Exposure

Capitalize on natural and experimental exposures to AChEi (OPs and Carbamates), emphasizing previously healthy populations. Some evidence already suggests they have similar problems; similar genetic risk factors.

Advantages:

- Can retrospectively assess for health problems (exposed-unexposed)
- Can prospectively assess for health problems (e.g. people entering pesticide field vs unexposed control) to define which PGW outcomes pertain. Can define susceptibilities (PON levels) without effect/cause contamination
- Can test PGW markers to define if marker is linked to AChEi exposure (or ill subset among AChEi exposed) in humans. (Provides a group without the full complex of alternative exposures -- vaccines, DU, combat stress)
- Can follow populations with known dose exposure (e.g. Bayer trial in Scotland) vs controls.
- If AChEi hypothesis is supported, implications directly extend to civilian & current military population

R 5

Develop a Brain Bank

Develop a brain bank, possibly contracting with existing banks for tissue preparation & banking.

Advantages: - Evaluate postmortem pathology.

- Test selected hypotheses about mechanism - change in abs. # & ratios of specific neuron and glial cell types, receptor binding sites...
- Can enlist veterans advocacy groups for help in collecting from deceased patients & friends/family (as controls).
- National VA system may assist uniform tissue collexn & preparation
- Commencing collection now will forestall delays later, as hypotheses "catch up"; otherwise, one is stuck with hypotheses and no tissue on which to test.
- Has provided important insights in Alzheimers, other

Disadvantages:

- Time lag till sufficient samples.
- Disparities in tissue collection/preparation.
- Costly

R 6

Genomic/proteomic screens

Conduct genomic & proteomic screens of ill PGWV vs controls, using gene arrays/ gene chips & analogous proteomic technology to identify patterns of markers that may statistically distinguish ill PGW veterans vs controls. Proteomic screens may be driven by experts/ hypotheses.

Advantages:

- May identify factors or factor clusters that distinguish ill PGWV vs controls (objective markers, even if based on a cluster)
- May identify factors or factor clusters that distinguish different illness subsets
- Illness subsets may emerge based on clustering in n-dimensional space
- Yield benefits for other illness conditions, to track treatments (proteomics)

Disadvantages:

- Cost
- "shot in the dark" - vs hypothesis driven markers

R 7

Treatment Trials

Support treatment trials of products that target mechanisms shown to be disrupted by AChEi (ACh mechanisms; mitochondrial mechanisms; oxidative injury/apoptosis; downstream products of ACh).

Support treatment trials for agents currently being used by ill PGW veterans.

Advantages:

- May lead to benefits to health in PGW veterans -- & others
- May save cost/ effort/ health by directing veterans away from treatments that are not useful, or harmful.

Disadvantages:

- Harm of treatments (for those with unfavorable safety profiles)
- ?Premature?

R 8

Choline

Choline: precursor to acetylcholine

Choline has direct alpha-7 nicotinic AChR binding

Choline and other alpha-7 agonists offers cytoprotection (protection against cytotoxicity) in a variety of experimental models in which cytotoxicity is experimentally induced.

Jonnala RR et al, Synapse 2003 47(4):262-9

R 9

Nicotinic Agonists: Nicotine

Nicotine has neuroprotective effects, possibly because it upregulates alpha-7 nicotinic receptors.

Terry AV et al 2002. J Pharmacol Exp Ther 2002. 301(1):284-92

R 10

Nicotinic Agonists: Nicotine

- Nicotine pretreatment reduces cell death caused by cytotoxic environment (deprive cells of NGF and serum).

- Protection is blocked if give selective alpha-7 blocker MLA (methyllycaconite).

- Other tested nicotinic agonists also are protective, though less so than nicotine*.

- The most protective ones increased labeled α-bungarotoxin binding sites the most - also suggesting again that upregulation of alpha-7 may be the mechanism

*The next most protective group among agonists tried included epibatidine, 4OHGTS-21, methycarbamylcholine, and 1,1-dimethyl-4-phenyl-piperazinium iodide.

Terry AV et al 2002. J Pharmacol Exp Ther 2002. 301(1):284-92

R 11

Nicotinic Agonists: Nicotine

Nicotine: improves attention and reduces distractibility in humans (literature in dementia and normals)

Nicotine normalized persistent deficits in memory function in rats previously exposed to repeated low level DFP.

Stone JD et al 2000. Brain Res 882 (1-2): 9-18.

R 12

Nicotinic Agonists: Nicotine

Nicotinic agents administered systemically have pain-relieving effects if there is nerve injury.

α4β2 subtype of nicotinic receptor was responsible, with nicotine; a different receptor with epibatidine.

Muscimol, a GABA agonist, also has this effect; and GABA blockers had opposite effect, suggesting the ACh-GABA system is responsible.

*Paw pressure test: reduces pain in animals with nerve injury but not normal animals.

Rashid Md. & Ueda H 2002. Brain Res 953: 53-62.

R 13

Nicotinic Agonists

SIB-1553A = an agonist of the human beta-4 nicotinic receptor: improved attention and reduced distractibility in rats with impairments in these areas (but not in normal rats).

*Impairment was produced by the NMDA antagonist dizocilpine

Terry AV et al 2002. J Pharmacol Exp Ther 2002. 301(1):284-92

R 14

Muscarinic M-1 Agonists

Talsaclidine: improve performance on a memory test* in rhesus monkeys, by 7-10%.

WAY 132983: improved performance on a memory test* in rhesus monkeys by 16%.

Comment: Different doses were optimal for different animals.

*Delayed match to sample

Terry AV et al 2002. Psychopharmacology (Berl) 162(3):292-300

R 15

ACH Agents

In animals: ACh enhancers (agonists, AChEi, etc) lead to:

- Improved cognitive function
- Pain relief
- Fatigue & weakness
- Protection of cells from ongoing injury

In humans:

- Improved cognitive function
- Pain relief
- Reduced fatigue/increased strength
- Benefits to GI fcn, sleep, mood being studied

R 16