Research Advisory Committee on Gulf War Veterans' Illnesses

June 28-29, 2004 Committee Meeting Minutes

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

DEPARTMENT of VETERANS AFFAIRS

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

I hereby certify the following minutes as being an accurate record of what transpired at the June 28-29, 2004, meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses.

_____

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

Table of Contents

Attendance Record

Members of the Committee in Attendance
James H. Binns, Chairman
Nicola Cherry
Beatrice Golomb
Joel Graves
Robert W. Haley
Marguerite Knox
William J. Meggs
Pierre J. Pellier
Steve Robinson
Steve Smithson
Lea Steele

Consultant to the Committee
Jack Melling

Committee Staff
Laura Palmer

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

Abbreviations

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

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

Meeting Agenda

Monday, June 28, 2004

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

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

Meeting Agenda

Tuesday, June 29, 2004

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

Welcome, introductions, and opening remarks

Mr. James H. Binns, Jr., Chairman

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

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

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

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

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

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

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

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

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

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

Chairman Binns thanked Dr. Greengard.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Chairman Binns thanked Dr. Findley.

WRIISC Research I: Overview of Completed and Pilot Studies

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

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

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

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

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

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

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

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

The meeting reconvened at 11:07 a.m.

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

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

WRIISC Research II: Ongoing studies

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

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

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

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

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

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

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

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

The meeting reconvened at 12:55 p.m.

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

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

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

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

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

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

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

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

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

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

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

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

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

Chairman Binns thanked Dr. Ciccone.

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

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

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

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

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

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

Chairman Binns thanked Dr. Chandler.

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

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

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

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

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

Chairman Binns thanked Dr. Helmer.

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

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

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

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

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

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

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

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

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

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

The meeting reconvened at 3:48 p.m.

Review of WRIISC Education/Risk Communication/Clinical Missions

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Clinical Evaluations of Gulf War and OEF/OIF Veterans

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

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

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

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

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

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

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

Overview and Discussion of Treatments for Unexplained Illnesses

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Update on VA ORD Gulf War Illnesses Research Initiatives and Activities

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

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

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

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

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

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

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

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

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

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

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

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

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

Chairman Binns thanked Mr. Kaplan.

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

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

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

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

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

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

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

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

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

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

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

Chairman Binns thanked Dr. Concato.

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

The meeting convened at 10:29 a.m.

Review of Recent Gulf War Research

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

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

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

Understanding the Neuronal and Biochemical Basis of Gulf War Illnesses

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

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

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

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

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

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

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

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

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

Chairman Binns thanked Dr. Fienberg and Dr. Mates.

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

The meeting reconvened at 1:42 p.m.

Committee Business

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

The meeting adjourned 2:52 p.m.

Appendix A
Presentation 1 – Benjamin Natelson

WRIISC Welcomes You

Good News!

We were officially informed two weeks ago that our application to establish a post-doctoral program in war-related illness was approved for two fellows

Road to the WRIISC

- 1974-1996 >> continuous MR funding in experimental behavioral medicine
  - Stress and serious medical illness
- 1989 >> started CFS Center at UMDNJ
  - Began unfunded pilots
- 1990 RFP to establish CFS CRCs
- 1991-2004 continuous funding (2 recompetes)
  - More than 125 papers published in this time

Road to the WRIISC

- 1993 >> RFP to establish CEHRs
- 1994-1999 NJ Gulf War Research Center
  - $500,000 + one FT MD for research only
  - 18 month recompetition process
  - Approved!! VACO decided not to refund!!!!
- 2000 >> Congress mandated WRIISCs
  - Modeled after GRECCs
    - $1,100,000 start up; $1,500,000 out years
      - Research only one of 4 equally important missions
      - Increased funding never given
    - Minimal research support (two 2-yr pilots)

WRIISC Construction Plan

- Included funds to set up "Restricted Living Center"
  - Allows environmental control
- Useful for research in small groups working in small spaces
  - Confinement (Tank Crews, POWs)
  - Military con-ops
  - Civilian first responders
  - Submariners
  - Astronauts on Mars mission
- Its existence will make us one of a kind for research funding opportunities

WRIISC Mission

- Clinical – Evaluate veterans with complex, hard to explain medical complaints
- Education – Educate veterans and health care professionals about medically unexplained fatigue and pain
- Risk Communication – Improve communication between veterans and health care professionals about medically unexplained symptoms; provide information on war related exposures
- Research – Develop comprehensive research program to understand/treat war-related illnesses

The Gap and Some Solutions

- Consequences of last minute funding cut
  - No treatment possible
  - No funds for veteran travel
  - Inadequate infrastructure to recruit subjects and support research
- Some possible solutions
  - Establish mini-grant program with $30K per year
  - VACO support of veteran travel
  - Ideas from you about how to find healthy controls

VA Research and the Doctor Today

- Physician-Scientist, a dying breed
- VA career development program, a life preserver for the academic physician
  - Guaranteed protected research time
- Huge changes in past 18 months
  - Heightened scrutiny and oversight; concerns about publicity; huge paperwork burden w/no support
  - Inadequate salary support (AI pays 5/8 of a salary)

CFS/FM in Civilians

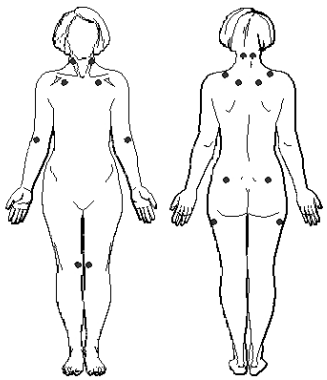
1988 & 1994 CFS Case Definitions

- 1988 - ↓ in activity by at least 50%
- 1994 – "substantial" decrease in activity
- Minor symptoms
  - Rheumatological; infectious; neuropsychiatric
- Exclusions
  - Obesity; any medical cause of fatigue
  - Bipolar; eating disorder; schizophreniform; alcohol or drug abuse

1994 Prevalence: ~0.4% of general population F>M

Minor Criteria to Diagnose CFS

1988	1994
sore throat	✓
tender lymph glands	✓
myalgia	✓
arthralgia	✓
unrefreshing sleep	✓
headache	✓
cognitive problems	✓
↑ Sx after exertion	✓
weakness	no
fever/chills	no

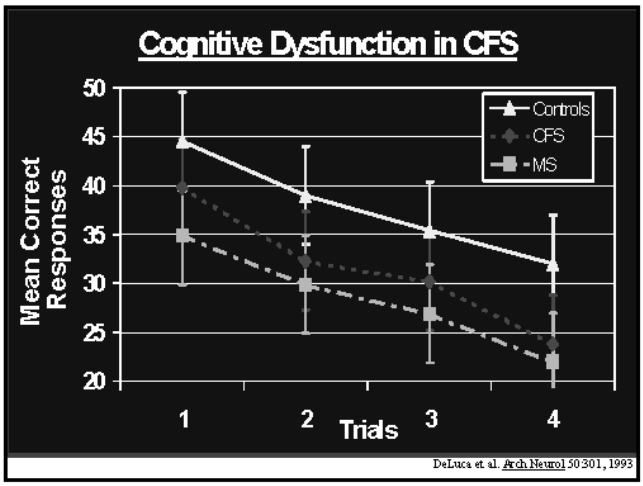


Rates of Comorbid Diagnoses

	CFS	CFS/MCS	CFS/FM	CFS/FM/MCS
Dx				
IBS	4/26 (15%)	2/11 (18%)	12/32 (38%)	10/18 (56%)
No Psych	35/62 (56%)	14/31 (45%)	17/44 (39%)	4/26 (15%)

Our Primary Hypothesis

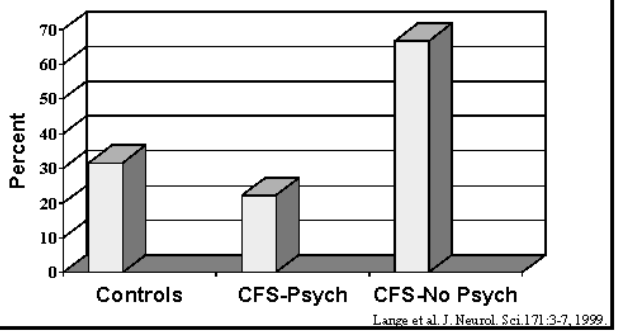
Some CFS patients may have an occult encephalopathy despite having no neurological findings other than occasional balance problems



Brain MRIs in CFS

- Do MRIs on CFS and sedentary controls
- Test hypothesis that the patients with no Axis I pathology will be the group with the highest frequency of brain MRI abnormalities

Percent of subjects with brain MRI abnormalities



Lange et al. J. Neurol. Sci.171:3-7, 1999.

Conclusions

- Stratification of CFS subjects is important to understand pathophysiology of illness
- CFS subjects without concurrent Axis I psychiatric disorder show significantly more
  - small abnormal MRI signal changes in subcortical white matter of frontal lobes

Supports conclusion that some CFS patients may have underlying encephalopathy

Where to go from here?

Examination of spinal fluid

Results

- LPs successfully done on 13 controls
  - None had protein >40 or > 3 WBCs/HPF
- LPs were successfully done on 39 CFS
  - 11 had elevated protein (≥ 45 mg/dl)
  - 4 had increased numbers of WBCs (> 5/HPF)
- Thus 39% of taps were outside of nl range!!

CFS Abnormality & Psychopath

- Of 28 CFS patients whose spinal fluid was normal – 8 had depression within a month of the psychiatric diagnostic interview (i.e., 29%)
- Of 15 CFS with spinal fluid abnormalities, none had current major depression ($p < .04$)
- However there were no differences in life time depression or in overall Axis I Dx

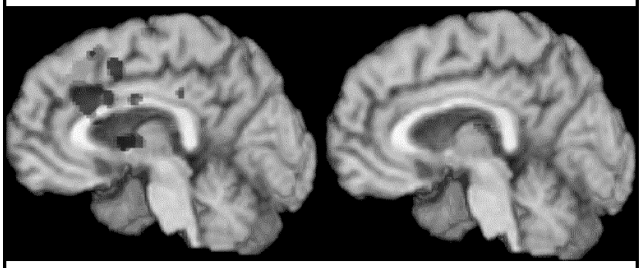
Conclusion

- Nearly 2/5 of all CFS patients tapped had spinal fluids outside of laboratory norms
  - Supports our inference that some patients with CFS have an occult encephalopathy
    - One confounding variable is drugs -- ???
  - We again found most CFS abnormalities in the group with no psychopathology
    - Continues to support our stratification strategy
  - Illness onset a predictor of pro-inflammatory IL-8

Use fMRI to Assess Brain Activity

- fMRI assesses Hb-O_2/Hb ratios to provide an indirect measure of neuronal activity
- This technique allows one to "see" the brain during various tasks and states
  - Study 1: Brain activation during warm and painful stimuli
    - FM and controls
  - Study 2: Brain activation during PASAT, a complex attentional task
    - CFS and controls with normal cognitive function

Warm non-painful stimulus



FM Group | Control Group

Cook et al., J. Rheumatology, in press.

What These Studies Tell Us

- FM patients feel warm "as if" it were hot
- CFS patients process information "as if" it were substantially harder than it really is
- The two studies suggest that CFS/FM brain requires additional neural resources to deal with mental processes that we take for granted
  - Is this the process responsible for mental fatigue?

A primary brain problem or not?

Look at the heart and determine if abnormalities exist and, if present, if they relate to any index of brain dysfunction

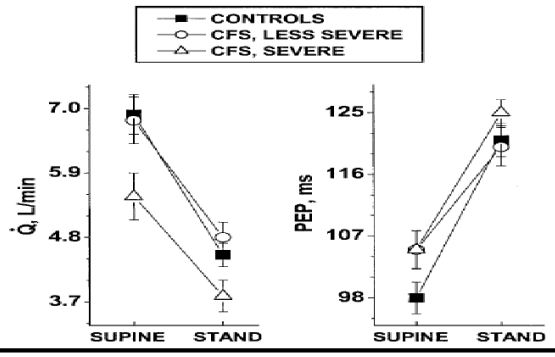
Non-Invasive CV Evaluation

• Assessed heart rate, blood pressure, and stroke volume in 17 CFS patients and 24 sedentary controls while supine, standing, and sitting

• Used impedance cardiography used to measure stroke volume -- an index of cardiac blood flow

Peckerman et al. *Am J Med Sci, 326:55, 2003*

Cardiac Output in CFS



Suggests that cardiac function is not normal – at least in the most severely affected patients

Research Question

Are CNS lesions secondary to perfusion problem or primary?

Conclusion

Data collected to this point supports our major hypothesis that CFS is for some a neurological disorder

Overlap with Sjögren's Syndrome

- Complaints of sicca common in CFS
  - May in part be due to use of TCAs
- Presence of Sjögren's antibodies very rare
- Lip biopsy is definitive way to Dx Sjögren's
  - We inquired about sicca, did Schirmer's tests, and biopsied 18 healthy controls and 25 CFS

Overlap with Sjögren's Syndrome

Gland Pathol Score	25 CFS Subjects				18 Controls	
	+ Symptom of Mucosal Dryness		– Symptom of Mucosal Dryness		– Symptom of Mucosal Dryness	
	Low Schirmer	Normal Schirmer	Low Schirmer	Normal Schirmer	Low Schirmer	Normal Schirmer
Normal	0	0	0	0	0	1
<1	2	3	0	12	1	16
≥1	8	0	0	0	0	0

Sirois et al. J Rheum 28:126, 2001

Presentation 2 – Tom Findley

Chemical Sensitivities

Fiedler 1996

- Persian Gulf Registry 1995
- 200 NE vets with, 228 w/out fatigue as medical complaint mail questionnaire
- 89% 63% fatiguing illness
- 39% 30% report chemical sensitivity
- 33 19% car exhaust
- 20 11% Perfume

Past Gulf War Research

Thomas Findley, M.D., Ph.D
WRIISC Associate Director for Research

Medical Evaluation of Vets With Fatigue, Chemical Sensitivity

Pollet 1998

- Medical exam of 72 complaints of fatigue, chemical sensitivity
  - Excludes self report of manic/depressive, schizophrenia, eating disorder, head trauma, age over 57
- 4 medical reasons for fatigue (3 focal weakness, 1 lyme)
- 15 psychiatric diagnoses (4 etoh, 7 mania, 3 schizo, 1 eating)
- 33 (62%) CFS
- 4 idiopathic CFS
- 14 cfs/mcs
- 6 mcs

- Veterans vs civilians with CFS,
  - Gradual onset (92 vs 21%)
  - Able to work (87 vs 54)
  - CFS severe (25 vs 61%)
  - Bed day/month (2 vs 3.5)
  - MCS also (29 vs 13%)

Prevalence of Chronic Fatigue and Chemical Sensitivity
Kipen 1999

- 68,000/700,000 GW vets in VA registry
- 2,011 randomly selected from 7 states; excluded persons in other major studies
- DE, IL, NJ, NY, NC, Ohio, PA
- 1161 (60%) response rate; 1000 answered CFS MCS questions (10% female)
- 34% CFS symptoms
  16% no other cause for fatigue
- 36% chemical sensitivity
  13% ≥ 3 lifestyle change
  OR 2 in women and African American

- No case definition for Gulf War Syndrome
- 16% VA gulf war registry meet CFS case definition
  - **Minimum 6 month fatigue**
  - **Substantial decrease in activity**
  - **At least 4 symptoms:**
    - Impaired memory or concentration
    - Sore throat
    - Tender lymph nodes
    - Muscle/multi joint pain
    - Headaches
    - Unrefreshing sleep
    - Postexertional malaise

Symptom Patterns
Hallman 2003

- 1161 responses
- 981 self reported medical problem due to gulf service
- Cluster analysis
- Mild illness in 60%
- Severe illness in 40%

- Factor analysis
- Mood memory fatigue – depression, anxiety, sleep
- Musculoskeletal - pain numbness in muscle or joint
- GI - abdominal pain, gas, diarrhea, nausea vomiting
- Throat breathing problems

Medical Followup

Natelson 2001

- **76 with CFS/ICF examined**
  - 34 axis I psychiatric illness beginning before GW
    - 31 continued after GW
  - 42 no axis I before
    - 21 developed axis I after
- **2 year followup**
  - 44 returned questionnaire
  - 13/26 came for repeat exam
  - symptom, symptom severity, job impact unchanged

Quantitative Sensory Testing

Peckerman 2000

- 29 GV with 1994 CDC CFS
  - 24% smokers
- 31 healthy GV
  - 3% smokers
- Vibration no difference
- Thermal no difference
- Tactile elevated in GV CFS compared to GV healthy;
- Both higher than civilian CFS healthy
- Higher tactile – self reported exposure to PB, burning human waste

Cardiovascular Response

Peckerman 2000

- 51 GV with CFS/ICF; 42 healthy GV
- Forehead cold pressor no difference
- Speech stressor
- Arithmetic stressor
- CFS GV little change in total peripheral resistance with cognitive stress
- Sedentary persons show heightened response to stress

Cardiovascular CFS and PTSD

Peckerman 2003

- **Subjects**
  - 55 GV with CFS (ICF)
    - 16 PTSD
    - 39 no PTSD
  - 47 healthy GV
- **Forehead cold pressor**
- **Speech stressor**
- **Arithmetic stressor**
- **Tilt table**

Aerobic Capacity

Nagelkirk 2003

- Background
  - No case definition for Gulf war Syndrome
  - Used CDC CFS case definition
  - CFS exercise capacity inconsistently reported – low or low normal
- Subjects
  - 15 GV with CFS (3 female, 12 male)
  - 19 control sedentary GV

- Procedure
  - Bicycle ergometer
- Results
  - Both CFS and controls in 10th percentile
  - Ve/O2 and Ve/CO2 at 0 watts higher in controls (lower O2 by 15%)
  - Ventilation at peak higher in controls (30%)
  - Trend to higher RER, workload (10%), HR (5%)

Perceived Exertion

Cook 2003

- Background
  - Perceived Exertion during exercise elevated in CFS
  - Lower maximum capacity
  - No elevation in RPE in exercise as a percent of peak capacity
  - VO2 max and VE same
  - 15 GV with CFS
  - 19 healthy GV

  - RPE elevated in GV CFS at both absolute and relative intensity
  - VO2 max similar, but ventilation VE 20% lower in CFS (-1 SD)

Muscle Function and EMG

Unpublished Data

- Background
  - Inconsistent nerve conduction and strength findings
  - Our finding of elevated sensory thresholds
  - 34 GV with muscle symptoms
  - 25 normal GV

- Decreased speed up and down stairs; walking
- EMG abnormalities 7/33 (21% vs 0%)
- 10 decreased interference pattern at maximum
- 5 increased polyphasic
- 6 decreased recruitment with increase in recruitment frequency
- 20% decrease in CSA in those with EMG change (similar to immobilization)

Fatigue and ACE Polymorphism

Vladutiu 2004

- Background
  - Myoadenylate deaminase (AMPD1)
  - Carnitine palmitoyltransferase (CPT)
    - Myopathies with pain, fatigue after exercise
  - I/D polymorphism in intron 16 of ACE gene (DCP)
    - I allele – decreased ACE activity, enhanced endurane
    - D allele – increased MI, CAD, LVH
      - DD 71% triple vessel, 54% single vessel CAD

- Study Population
  - 61 nonveterans with CFS (mostly female)
  - 49 veterans with ICF or CFS
  - 45 healthy Nonveterans
  - 30 healthy veterans

- Results
  - AMPD1, CPT – no difference or trend between groups
  - DCP
    - 85% D allele, 78% DD in veterans with ICF, CFS
    - 50% D allele in normal veterans, CFS and normal non veterans

Psych Diagnoses

Lange 1999

- 47 healthy
- 100 fatigued GV from 10 states, GW registry

- 17 medical cause for fatigue
- 19 Etoh, schizo, mania eating disorder

- 53 CFS, ICF, MCS
- 42 healthy

- CFS 62% Axis I – 36% depression, 21% PTSD, phobias
- CFS 40% more than one DX
- Healthy 14%

PTSD

Natelson 2001

- 76 CFS, ICF GV

- 50% PTSD

- PTSD
  - Kang 2003
  - 11,000 GV
  - 9,000 non GV

Stressors

Fiedler 2000

- 164 vets with fatigue examined
- 45 healthy GW Vet
- 35 CFS with psych
- 23 CFS no psych

- CFS vs healthy
  - More stressors during and after the war
  - More negative coping strategies
  - More neuroticism, defensiveness

- Self reported stressors

Cognitive Function

Lange 2001

- 39 healthy
- 48 GW vet with fatigue
  - 27 CFS
  - 17 CFS MCS
  - 4 MCS
  - 42% Major depressive disorders
  - 29% Anxiety disorders
  - 21% PTSD

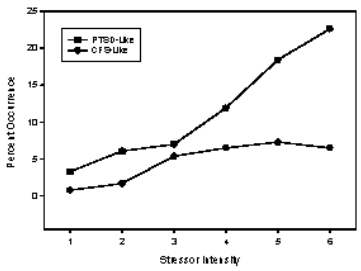
- 25% increase simple reaction time
- 10% increase complex reaction time
- Digit span backwards
- PASAT
- Trail making test

- Effect of mental disorders
- Depression – decreased simple and complex reaction time, PASAT
- Anxiety – PSAT
- PTSD – not related
- GWI still associated with simple reaction time; not complex or PASAT

PTSD

Kang 2003

- 700,000 deployed to gulf
- 800,000 not deployed to gulf
- Sampling stratified by sex, active/reserve/natl guard, branch of service
- 15,000 deployed GW vets
- 15,000 non gulf vets
- 70% response rate



- CFS 5.6% vs 1.2%
- PTSD 12% vs 4.3%
- Combat exposure – chemical gear or alarm, witness death, actual combat
- PTSD increases with increased combat
- CFS does not
- Both increase if national guard activated or deployed to gulf

Immune Function

Zhang 1999

- 43 GW vet with CFS (31 Axis 1)
- 34 healthy GW vet (6 axis 1)
- 68 civilian with CFS (33 axis 1)
- 53 healthy civilian (0 axis 1)

- No changes in civilians with CFS
- Veterans with CFS show type 1, inflammatory response
  - More total and % T cell
  - More total and % MHC II+ T cell
  - Less percent NK cells
  - Higher IL-2, IL-10, IFN-gamma, TNF-alpha
  - Trend to higher IL 4, LI 6, LI 12

Immune and Cognitive Function

Brimacombe 2002

- 40 GW vet with CFS
- 33 health GW vet
- 28 civilian with CFS
- 31 healthy civilian

- Immune function related to CFS
- Reaction time higher in GW and civilians with CFS
- Only lymphocytes significant (.06) when reaction time included in model
- Education and reaction time most significant

- SF36 general health, physical function, mental health, social function
- Education and reaction time highly related in veterans with CFS
- Only reaction time in civilians for all but mental health
- TH2 and lymphocytes related to SF36 in vets
- Only lymphocytes remain when reaction time included

Presentation 3 – Dane Cook

Pain sensitivity in Gulf veterans with medically unexplained musculoskeletal pain

(DVA # 561-00215)

Dane B. Cook, PhD
Health Science Specialist
WRIISC
East Orange VAMC

The Problem

- **Unexplained muscle pain is a serious problem for many Gulf veterans (GVs)**
  - 4th most frequently reported symptom (IOM report, 1996)
  - Reported twice as frequently in GVs than non-GVs (Kang et al., 2000)
  - Serious adverse consequences on the veteran's personal and professional lives (Kang et al., 2000)

The Problem

- **Numerous studies have been conducted describing the problem**
- **Little research aimed at determining the cause**
  - There is a need for research aimed at understanding the causes of unexplained pain in GVs

Previous Research

- **Civilians with Fibromyalgia:**
  - More sensitive to experimental pain
    - **(Cook et al., 2004; Kosek et al., 1996; Lautenbacher et al., 1994)**
  - Lack normal inhibition of pain
    - **(Kosek, Hansson, 1997; Lautenbacher, Rollman, 1997; Staud et al., 2003b)**
  - Exaggerated brain responses to sensory stimuli
    - **(Cook et al., 2004; Gracely et al., 2002)**
  - Enhanced pain during exercise and increased pain sensitivity following exercise
    - **(Mengshoel et al., 1995; Vierck, Jr. et al., 2001)**

Purpose

- **Comprehensively assess pain:**
  - Look at different dimensions of pain (intensity & affective)
  - Look at experimental and naturally occurring pain
    - Natural muscle pain, heat, pressure
  - Examine pain pre and post exercise
- **Test potential mechanism:**
  - immune system and pain (**in progress**)

Hypotheses

- **GVs with medically unexplained muscle pain will:**
  - Be more sensitive to painful stimuli pre and post exercise compared to healthy GVs
  - Have increased sensitivity to painful stimuli following exercise
  - Show a positive relationship between the immune system and pain (**in progress**)

Method

- **N = 34 participants**
  - n= 14 GVs with unexplained muscle pain
    - Pain in muscle and joints (more than one body quadrant)
    - > 3 months
    - Intense severity
  - n= 20 healthy GVs without pain
- **Testing to occur on 2 separate days**
  - Maximal exercise and pain testing
  - Submaximal exercise testing, pain testing and blood sampling

Method

- **Experimental Procedures:**
  - Psychophysical pain assessment
  - Exercise @ 70% of peak oxygen consumption for 30 minutes followed by 5 minute active recovery
  - Psychophysical pain assessment

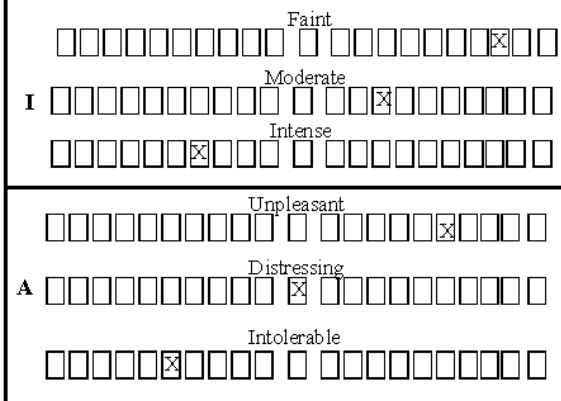
Method

- **Psychophysical Pain Assessment:**
  - Heat pain thresholds – thenar eminence non-dominant hand
  - Pressure pain thresholds – second digit of dominant index and middle fingers
  - Supra-threshold pressure pain ratings
  - Supra-threshold heat pain rating (volar forearm)
    - Descriptor Differential Scales

Method

- **Descriptor Differential Scales**
  - Based on psychophysics of cross-modality matching
  - Assess both intensity and affective pain dimensions
  - Several descriptors presented in random fashion
  - Ratings across a 21-point continuum
  - Similar to ratio scaling procedures (curve estimation)
  - Provides a measure of internal consistency

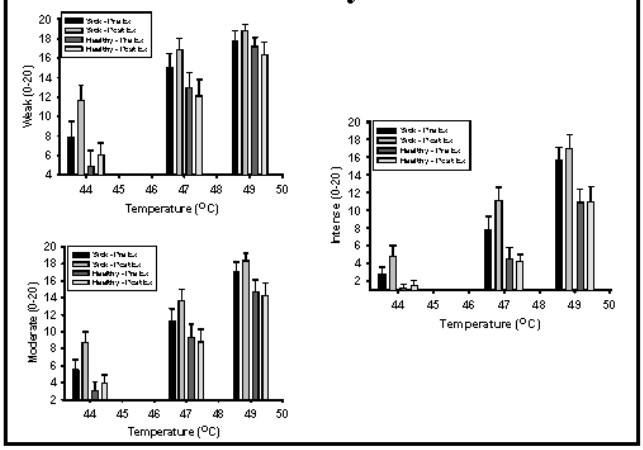
Descriptor Differential Scales



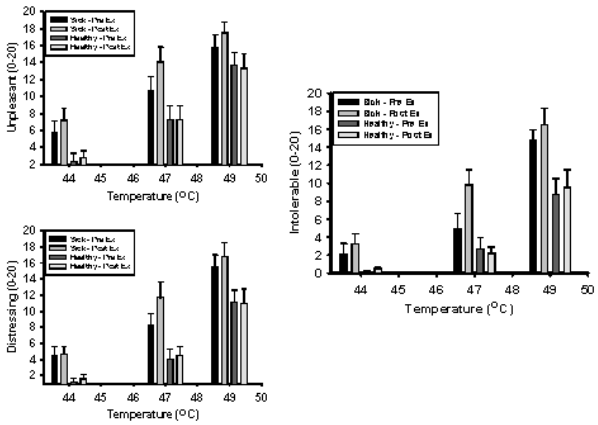
Results

	Sick GVs (n=14)	Healthy GVs (n=20)
Age (yrs)	39.0 ± 7.1	40.4 ± 7.9
Height (cm)	176.5 ± 8.3	168.4 ± 28
Weight (kg)	96.0 ± 24.7	90.4 ± 13.9
HR (b·min^{-1})	74.0 ± 12.0	65.0 ± 8.0
SBP (mmHg)	117.4 ± 9.1	117.6 ± 10.6
DBP (mmHg)	74.8 ± 6.7	77.5 ± 6.8
Peak VO_2 (ml·kg·min^{-1})	28.7 ± 7.5	32.1 ± 8.2
Submax VO_2 (ml·kg·min^{-1})	17.8 ± 4.4	21.9 ± 5.3
% peak VO_2	63.0 ± 0.06	68.0 ± 0.03
HPT (°C) Pre Ex	43.7 ± 4.2	44.2 ± 3.2
HPT (°C) Post Ex	44.2 ± 3.8	45.0 ± 2.7
PPT (sec) Pre Ex	31.0 ± 31.8	46.0 ± 40.1
PPT (sec) Post Ex	38.8 ± 44.5	49.5 ± 37.3

DDS Intensity Results



DDS Unpleasantness Results



Discussion of preliminary findings

- **GVs with medically unexplained musculoskeletal pain:**
  - Are more sensitive to experimental pain stimuli than healthy GVs
  - Describe experimental pain stimuli as more intense and more unpleasant following 30 minutes of moderately intense submaximal exercise
  - Surprisingly, healthy GVs did not exhibit an exercise-induced analgesic response

To be determined

- What is the relationship between pro-inflammatory cytokines and pain sensitivity in GVs with medically unexplained muscle pain?
- What is the relationship between naturally occurring muscle pain during exercise and pain sensitivity post exercise?
- What are the spinal and supraspinal mechanisms underlying pain sensitivity and painful symptoms in GVs with medically unexplained muscle pain?

Presentation 4a – John Ottenweller

Plasma Cortisol, Paraoxonase and Butyrylcholinesterase in Gulf War Era Veterans

John E. Ottenweller, Benjamin H. Natelson, Quanping Zhu, Chin-Lin Tseng
EOVAMC

Domenic Reda, Kwan Hur, Renee Alpern
Hines Cooperative Studies Program

The National Health Survey of Gulf War Era Veterans and their Families

693,000 Gulf Vets (GVs) and 800,000 non-Gulf Vets (NGVs)

Phases I and II

- Stratifed Random Sample of 15,000 Gulf Vets and 15,000 non-Gulf Vets
- Phase III (1999-2001)
- 5885 random subsample stratified to select veterans close to study sites
- 1996 GVs and 2883 NGVs invited for study

Phase III of the NHS

1061 GVs (53%) and 1128 NGVs (39%) participated

Demographics

- 78% Male
- 78% Caucasian
- 48% Smokers
- 98% had more than a high school education

Phase III of the NHS

Service Characteristics

- 35% Guard/Reserve and 65% Active Duty Troops
- 75% Army and 25% Other Services
- 17% Officers and 83% Enlisted Men

Status for Diseases Tested in Models

- 23% Severe Chronic Multisymptom Illness (CMI)
- 3% PTSD in year before examination

Only 1.6% CFS, so to few to include in model

Data Collected in Phase III But Not in Final Model

CMI

- CMI by itself (univariate analysis) associated with significantly lower cortisol levels

Combat Exposure Scale (Proctor)

Beck Anxiety Inventory

PTSD (CAPS)

Smoking

Summary I

Greater fatigue is associated with lower cortisol levels, but CMI was not in the final model.

At lower BDI scores, more PTSD symptoms lead to higher cortisol levels. At higher BDI scores, more PTSD symptoms lead to lower cortisol levels.

Guard/Reserve veterans have lower cortisol levels than Active Duty veterans.

GVs have lower cortisol levels than NGVs

- Marginally significant interaction between Duty Type and Deployment, so that their main effects are largely driven by lower cortisol levels in deployed Guard/Reserve veterans.

Samples from Case-Control studies involving NJ CEHR, OR EHRC and CDC

Blood samples were collected from GVs with unexplained illnesses or healthy GVs at the East Orange VA, the Portland VA and from the Pennsylvania Air National Guard cohort studied by the CDC (Fukuda).

Summary II

In older GVs, poorer mental functioning was associated with lower cortisol levels.

Lower mental and social functioning were associated with lower cortisol levels, better functioning in either domain was associated with higher cortisol levels.

Cortisol Levels in NJ and CDC Subsample

Only the NJ and CDC datasets (not OR) had physician diagnoses of CFS and Depression.

Summary III

The combination of depression and CFS resulted in much lower cortisol levels than either CFS or depression alone.

Conclusions

Increasing fatigue, and the combination of greater depression and higher PTSD symptoms were associated with lower cortisol levels.

The combination of poorer mental and social functioning was also associated with lower cortisol levels.

Guard and Reserve veterans who were deployed were at greater risk of lower cortisol levels than deployed Active Duty veterans or NGVs

In deployed veterans, the combination of CFS and depression resulted in lower cortisol levels.

Final Message

Something about service in the first Gulf War resulted in lower cortisol levels 8-10 years later, and Guard/Reserve troops were at greater risk.

These lower cortisol levels were associated with increased fatigue, more depressed mood, more PTSD symptoms, and poorer mental and social functioning. Greater allostatic load seemed to be associated with lower cortisol levels.

If low cortisol levels are contributing to some of these symptoms, rather than a result of them,

low-dose glucocorticoid therapy might improve the health and well being of symptomatic veterans with low normal levels of cortisol.

Plasma BuChE in Gulf Era Veterans

BuChE is a plasma enzyme that binds anti-cholinesterases and prevents them from inactivating acetylcholinesterases in synapses and the neuromuscular junction.

Genetic variants with point mutations in the binding site result in lowered affinity.

Reduced activity may result in increased sensitivity to anticholinesterases and neurotoxins.

BuChE Phenotypes

Plasma BuChE activity was measured in the NHS samples from GVs and NGVs.

We were not allowed to measure phenotypes because the consent for the NHS excluded genetic testing.

So we were not able to determine whether BuChE phenotype was associated with illness.

Univariate Analyses of BuChE Activity

Greater fatigue and poorer quality of life were associated with higher BuChE activity.

Better scores on the physical component summary scale of the SF-36 were associated with lower BuChE activity.

Summary of BuChE Analysis

More combat exposure associated with greater BuChE activity.

But an interaction between combat exposure and the physical component summary of the SF-36.

- In those with low combat exposure, lower PCS scores associated with lower BuChE activity.
- In those with high combat exposure, lower PCS scores associated with higher BuChE activity.

Conclusions

We hypothesized that lower BuChE activity would be associated with poorer health in GVs, but it was not.

In nGVs, lower BuChE activity may be associated with poorer physical functioning.

Maybe exposure to anticholinesterases needs to be added to the regression model.

Presentation 4b – John Ottenweller

Paraoxonase Activity in Gulf Era Veterans

Paraoxonase (PON1) is a plasma protein produced by the liver that degrades a number of organophosphates including pesticides and nerve agents (sarin).

There are common genetic variants that alter the affinity of the enzyme for its substrates.

- A substitution at position 192 (R allele) reduces metabolism and increases toxicity of pesticides.

Genetic Variants of PON1

We were not allowed to measure the PON1 phenotypes because the consent in the NHS did not allow genetic testing.

Instead we measured activity in the presence of 1 M NaCl, which we found was able to separate phenotypes relatively well.

- Lowest PON1 levels associated with QQ phenotype, intermediate levels with QR phenotype and highest levels with the RR phenotype

Control of PON1 Activity

PON1 activity depends on genetic variants.

PON1 activity depends on enzyme protein levels.

- Liver and kidney disease lower PON1 levels.
- Smoking and alcohol use lower PON1 levels.
- PON1 levels are affected by diet.

Univariate Analyses of PON1

Those with PTSD had lower PON1 activity.

- As PTSD symptoms increased, PON1 activity decreased

Those with more combat exposure had lower PON1 activity.

Lower PON1 activity was associated with poorer mental functioning.

Summary of PON1 Results

Those with CMI have higher PON1 activity.

- Increase is greater in those with PTSD.
- Increase is less in GVs than NGVs.

Without CMI, increasing PTSD symptoms lead to lower PON1 activity. Decrease greater in those with CMI.

Decrease in PON1 with increasing combat exposure was greater in those with PTSD.

Interactions with education questionable because only 41 veterans had just a high school eduction.

Conclusions about PON1

Likely genetic influences:

- Non-caucasians are more likely to have R allele.
- Risk of CMI increased in those with R allele
  - However, risk was less in GVs.

Likely environmental influences:

- Aging leads to lower PON1 activity.
- Greater combat exposure and more PTSD symptoms lead to lower PON1 activity.

Collaborators

East Orange VA
- Benjamin Natelson
- Chin-ling Tseng
- Malvin Janal
- Guanping Zhu
- Jennifer Nelson

Hines VA CSP Center
- Domenic Reda
- Renee Alpern
- Kwan Hur
- Tammy Nydam
- Mary Ellen Vitek

Portland VA
- Peter Spencer
- Linda McCauley
- Mohammad Sabri
- Andrew Bacelis

St. Louis VA
- Seth Eisen
- Melvin Blanchard

CDC
- William Reeves
- Rosane Nisenbaum

VACO & Washington VA
- Han Kang
- Clare Mahan
- Frances Murphy

Boston VA
- Donald Humphries

Presentation 5a – H. Liesel Copeland

Development of a Risk Perception Questionnaire for Military Personnel

- Principal Investigator: Susan Santos
- Co-Investigators:
  - Drew Helmer
  - Kimberly Price
  - Liesel Copeland

Rationale

- **The perception of risk impacts:**
  - Communication (Provider-Patient, System-Individual)
  - Focus on educational material
  - Health
- **To appropriately respond to the concerns of veterans, need to know their beliefs and understanding**
- **Risk Communication questionnaires have been developed for the general public, and a good understanding exists of the perception of many environmental risks. YET nothing exists for military personnel and military exposures**

Project

- **Objective:**
  - To develop a robust questionnaire that measures the extent of perceived risk from military exposures
- **Steps:**
  - Utilize literature and experts to develop draft items
  - Conduct focus groups and interviews to test items utilizing cognitive approaches
  - Conduct psychometric analysis on items
  - Combine qualitative and psychometric data to finalize instrument
  - Validate instrument on large sample

Presentation 5b – H. Liesel Copland

Evaluating a bio-terrorism preparedness campaign for veterans

- Local Principal Investigator: Liesel Copeland
- Principal Investigators: John Fotiades, Matthew Friedman
- Sites:
  - VISN 3, VISN 4, VISN5, VISN16, VISN21, VISN22

Rationale

- Greatest payoff in fighting bio-terrorism lies in improving our response by being prepared
- The majority of existing educational and preparation material is targeted for providers or emergency responders
- This project aims to close the gap by producing materials for the public, beginning with veterans.

Objectives

- 1. To develop educational material for veterans which will provide information about bio-terrorism and coping mechanisms for dealing with such a disaster.
- 2. To evaluate using a study-developed survey and other measures the effectiveness of such material in improving knowledge, coping mechanisms and confidence in the VA as well as decreasing anxiety over a future occurrence.
- 3. To compare the overall effectiveness of such material when delivered to veterans via the Internet as opposed to a standard printed version.
- 4. To establish a mechanism allowing for the future comparison of health care utilization patterns in response to a bio-terrorism disaster in those veterans receiving the education and improved survey scores with those with no improved scores

Project Phases

- Conduct focus groups with veterans to identify content areas
- Develop and pilot questionnaire
- Write materials, review with ID experts, MH experts, Risk communication experts, Patient Ed experts
- Pilot test educational materials in focus groups
- Administer materials in hospital and community based settings with VA and non-VA user veterans. Utilize pre-post questionnaire.

Presentation 5c – H. Lisel Copeland

Process Evaluation of the PTSD clinical practice guideline for veterans

- Principal Investigator: H. Liesel Copeland
- Co-Investigators:
  - WRIISC: Drew Helmer
  - National Center for PTSD: Josef Ruzek
  - Washington DC VA: Robin Peck
  - Indianapolis VA: Matt Bair
  - Columbia MO VA: Ayyasamy Panneerselvam
- Proposal to Gulf War RFA

Rationale

- Gulf War veterans have a three-fold higher incidence of PTSD than veterans of the same era not deployed to the gulf. Prevalence is similar to Vietnam veterans.
- PTSD is under-recognized in primary care.
- The VA recently released an evidence-based clinical practice guideline for PTSD
- Adoption of the guideline could improve clinical care.
- There is a need to evaluate the extent of implementation (awareness and adoption) of the guideline in primary care settings

Specific Aims

- Elucidate primary care providers' knowledge, needs, attitudes, beliefs, and intentions about he CPG for PTSD
- Describe patients' responses to assessment of key components of the PTSD CPG
- Identify documentation of diagnosis and care of patients with PTSD in the medical records
- Compare the three perspectives (clinician, patient, chart documentation) of need and utility for the PTSD CPG

Data Collection

- Multi-method data collection with triangulation of sources
  - Interviews of Primary Care providers
    - Knowledge, perceptions, use
  - Questionnaires of Primary Care providers
    - Knowledge, perceptions, use
  - Questionnaires of Patients
    - Symptoms, provider communication, recall of screening
  - Medical Record review
    - Implementation – diagnosis, key guideline steps

Presentation 6 – Benjamin Natelson

Stress Responses in Gulf War Veterans

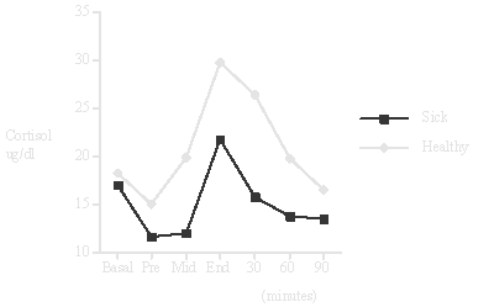
Principal Investigator: Benjamin Natelson, MD

Director
War Related Illness and Injury Study Center
Department of Veterans Affairs

Disorders associated with blunted HPA activity

- PTSD (Yehuda 2002)
- Chronic fatigue syndrome (Gaab 2002)
- Rheumatoid arthritis (Cutolo 2003)
- Chronic pain (Tennant 2001)

Plasma cortisol response to exercise was blunted in GVs with medically unexplained illness



MERIT: Pituitary-adrenal function in GVs with medically unexplained illness

- Study 1: Adrenal volume
  - » Long-term picture of activity of the adrenal gland.
- Study 2: HPA Negative feedback effects
  - » How well are stress responses turned-off?
- Study 3: Activation of the HPA axis
  - » How well are stress responses turned on?

Study 1: Adrenal volume in GVs with medically unexplained illness

Adrenal volumes will reflect the long-term consequences of HPA activity since ACTH stimulates the growth of this gland

- Axial MRI of adrenal glands using 5 mm slices

Study 2: Negative feedback effects of cortisol in GVs

Blunted HPA activity in GVs may result from greater negative feedback effects of cortisol

- Metopirone to shut off adrenal gland followed by hydrocortisone infusion.
- Blood samples assayed for ACTH

Expected results

- Greater suppressive effects of hydrocortisone on plasma ACTH concentrations in sick GVs
- This would provide indirect evidence for altered glucocorticoid receptor density in the brain (i.e.. hippocampus)

Study 3: Central drive on HPA axis

Blunted HPA activity in sick GVs may be caused by reduced activation of the HPA during stress

Insulin induced-hypoglycemia with clamped and stepwise clamped glucose

- Blood samples assayed for ACTH

Expected results

- ACTH responses to insulin-induced hypoglycemia will be lower in GVs with unexplained illness
- This result would suggest impaired centrally-mediated activation of the HPA during stress

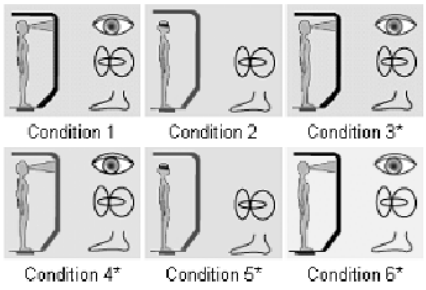
Conclusions

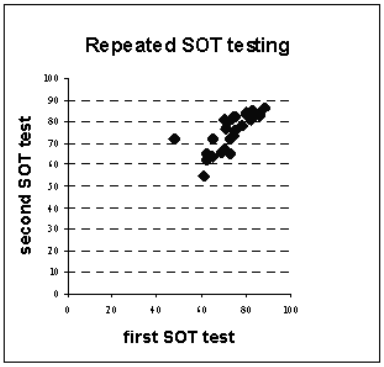
- Origins for altered HPA activity can occur at the level of the adrenal gland, hypothalamus, pituitary or higher brain regions.
- This series of studies will test axis function at all levels in an attempt to locate the source of altered HPA activity in GVs with unexplained illness
- These results will improve our understanding of the pathophysiology of the GVs health complaints

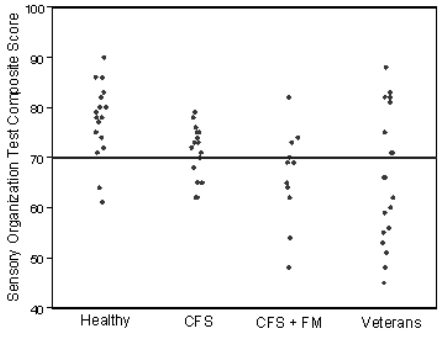
Presentation 7 – Tom Findley

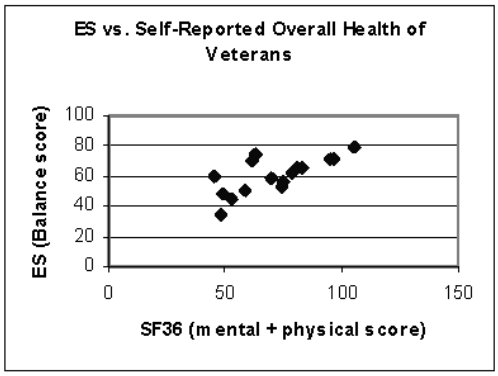
Pilot Data on Balance in Unexplained Illness

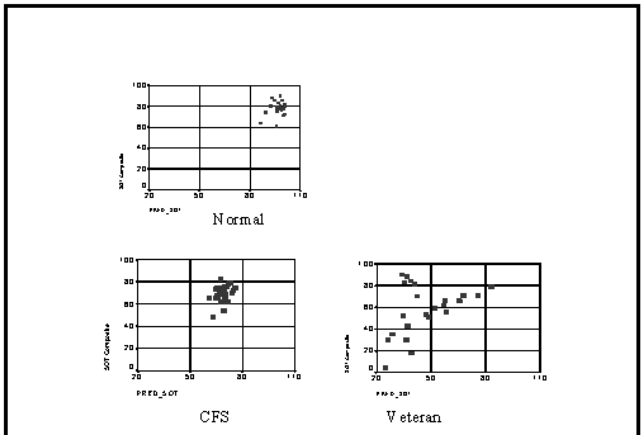
Principal Investigator: Thomas Findley, MD, PhD
Co-investigator: Karen Quigley, PhD

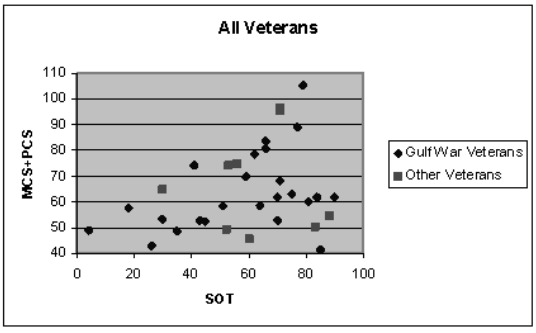












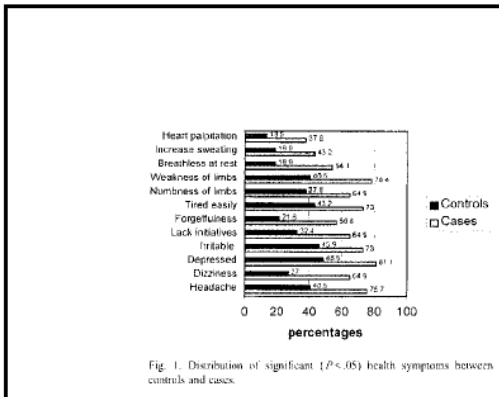
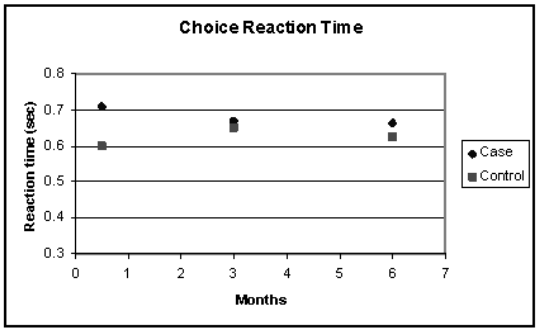


Fig. 1. Distribution of significant ($P < .05$) health symptoms between controls and cases.

- Self reported disease and SOT and SF36
- Self reported lung problems
  - Correlates negatively with SOT (r-sq = -.428, p < .021)
- Self reported depression
  - Negative correlation with SOT (-.436, P, .016) and total SF (-.576, p < .001)



Presentation 8a – Karen Quigley

Risk Perception and the Psychobiological Sequelae of Vaccination

Principal Investigator:

Karen Quigley

Co-Investigators:

Susan Santos

Drew Helmer

Chin-Lin Tseng

Key Questions

How are risk perceptions of a bioterror agent vaccine affected by high or low information (i.e., optimized vs. non-optimized) risk communications?

How is vaccine response altered by a threatening context during vaccination and what role do vaccine-related symptoms and enhanced sympathetic arousal during vaccination play in that response?

Are the chronically distressed (high trait negative affect) at higher risk for vaccine-induced distress, more symptoms and lower vaccine efficacy with a threatening (i.e., bioterror) vaccine?

Preliminary Results

• We have conducted 3 focus groups to begin creating the optimized vaccine information sheet (VIS) which will be compared to the standard CDC VIS in Study 1.

•We will soon be conducting 2 additional focus groups that will help us to assess the clarity, comprehensiveness, appeal, and framing of two potential optimized VISs.

Experimental Plan

•Study 1: Focus groups used to design and test an optimized risk communication (i.e., VIS)

•Study 2: Compare risk and benefit perceptions of vaccines and other agents across high and low anxious groups receiving either a standard or optimized VIS with expectation of either a usual flu or possible bioterror flu

•Study 3: Compare symptoms and vaccine efficacy across high and low anxious groups receiving either a placebo, a flu vaccine or a vaccine described as protection against a possible future bioterror flu

Presentation 8b – Karen Quigley

Prospective Study of Functional Status in Veterans at Risk for Medically Unexplained Symptoms

Principal Investigator:
Karen Quigley

Co-Investigators:
Shelley Weaver
Chuck Engel (Walter Reed and USUHS)
Ashok Poluri
Karen Raphael (NJ Med. School)
Chin-Lin Tseng
Patricia Findley

Objectives

1. To determine prospectively the pre-deployment and immediate post-deployment risk factors (such as trait negative emotionality and prior trauma) that predict later medically unexplained symptoms (MUS) and poor functional status

2. To determine prospectively the pre-deployment and immediate post-deployment resilience factors (such as coping style and social support) that predict later medically unexplained symptoms (MUS) and poor functional status

3. To improve on previous design problems (recall bias, selection bias and lack of effective baselines) in studies of MUS

Preliminary Results

•Finishing a pilot study (currently 14 subjects tested) to determine the feasibility of and time required for the self-report and physiological measures (reactive salivary cortisol and cardiac autonomic function)

•Developed a computer program that presents all questionnaires to the subject for direct data entry via a mouse & keyboard

•Developed an Access database (including automated data import and report generation) for all self-report variables

Experimental Plan

•Prospective, longitudinal observational study

•Predictors: Negative emotionality, dissociative tendencies, social support, coping skills, current symptoms, cortisol and cardiac autonomic stress reactivity (to a 14 minute combined mental/physical stressor)

•Outcomes: SF-36 Mental and Physical Component Summary scores, healthcare utilization, chronic multisymptom illness status (using CDC case definition)

•Controls: Prior trauma, PTSD symptoms, current distress, body mass index, prior environmental exposures, age, gender, education

Presentation 9 – Dane Cook

Functional Imaging of Pain in Veterans With Unexplained Muscle Pain

Principal Investigator: Dane B. Cook, PhD

Co-Investigators:

NJ WRIISC: Benjamin Natelson, MD

UMDNJ-NJMS: Bharat Biswal, PhD and Wen-Ching Liu, PhD

Rationale

Unexplained muscle pain is a serious problem for many Gulf Veterans (GVs)

- 4th most frequently reported symptom (IOM report, 1996)
- Reported twice as frequently in GVs than non-GVs (Kang et al., 2000)
- Serious adverse consequences on the veterans personal and professional lives (Kang et al., 2000)

Numerous studies have described the problem, however little research aimed at determining cause

Key Questions

Are GVs with unexplained musculoskeletal pain more sensitive to experimental pain stimuli compared to healthy GVs and GVs with rheumatoid arthritis (RA)?

Do GVs with unexplained muscle pain exhibit an exaggerated brain response to sensory stimuli compared to controls?

Do GVs with unexplained muscle pain fail to exhibit activity in brain areas known to be involved in pain inhibition or modulation?

Design

- **N=54 Participants**
  - n=18 GVs with unexplained muscle pain
  - n=18 GVs with RA
  - n=18 healthy GVs
- **Testing over 2 days**
  - Day 1 = pain sensitivity testing and MRI training (Mock MRI at WRIISC)
  - Day 2 = brain imaging while receiving painful and non-painful stimuli

Analysis

- Sensory data will be examined for group differences and psychophysical curve estimates will be used to determine pain sensitivity in GVs
- fMRI data will be processed and analyzed using statistical parametric mapping techniques (SPM)
- Whole brain and region of interest analyses will be used to determine CNS sensitivity and nociceptive modulation in GVs with unexplained muscle pain compared to healthy and RA GVs

Presentation 10 – Don Ciccone

On-Line Treatment for Veterans with War-Related Multisymptom Illness

Principal Investigator: Donald S. Ciccone, Ph.D.
Co-Investigator: Helena K. Chandler, Ph.D.

Background

- As far back as the American Civil War, soldiers have reported nonspecific ailments that could not be attributed to an underlying medical cause.
- The prevalence of GWI or similar symptom-based illness may be as high as 45% to 60% in deployed personnel. (Fukuda et al, 1998; Baker et al, 1997, Wolfe et al, 2002)

Background (continued)

- Despite an uncertain etiology, GWI and other symptom-based ailments have substantial consequences for veteran health:
- Frequent VA medical visitation
- Physical disability
- Psychological distress/psychiatric morbidity.

Study Rationale

- In order to address the anticipated increase in GWI, new and more efficient treatments are urgently needed to augment or replace standard VA care.

Rationale for Telemedicine

- Fortunately, an effective treatment using cognitive-behavioral techniques (CBT) has been developed to ameliorate symptom-related distress and reduce unnecessary healthcare utilization.
- Despite evidence of CBT efficacy provided by RCTs, a major limitation is that patients are often nonadherent. Only 38% were adherent in a recent large scale trial of CBT.
- Clinical effectiveness of CBT is undermined if fewer than half of those who need treatment are likely to attend.

A Randomized Trial of Telemedicine

- The proposed study will address this public health problem by testing a novel treatment for GWI-On-Line CBT using instant voice messaging (voice stream technology).
- Treatment is administered over the Internet and allows veterans to speak with CBT practitioners in real time just as they would on the telephone.

Study Aims

Aim 1. Determine the efficacy of On-Line CBT for veterans with GWI who are frequent consumers of ambulatory medical care.

Aim 2. Determine whether CBT for veterans with GWI leads to a reduction in the cost of VA healthcare

Study Design

150 High utilizing veterans will be assigned to one of three study conditions:

I On- Line CBT + Customary Medical Care (N=50)
II In-Person CBT + Customary Medical Care (N=50)
III Customary Medical Care Only (N=50)

Study Design

- Intent-To-Treat Strategy
- Primary Outcome: Utilization of VA medical services
- Assessment Protocol: Electronic chart review 1 yr before and 1 yr after treatment

VA Significance

- The proposed study is intended to reduce unnecessary VA utilization while preserving or improving physical function, patient satisfaction and other quality of life indicators.
- Treatment can be made readily available to veterans regardless of their geographic location.

Long Term VA Benefits

Long-term benefits may also include:

- Lower costs for medical care
- Improved allocation of VA resources
- Improved quality of life for GWI veterans
- Less psychiatric morbidity
- Lower risk of iatrogenic injury.

Presentation 11 – Helena Chandler

Internet Disclosure Treatment for Multisymptom Illness

Principal Investigator:
Helena K. Chandler, Ph.D.

Co-Investigators:
Benjamin H. Natelson, M.D.
Donald S. Ciccone, Ph.D.

Funding: Agency for Healthcare Research and Quality

Background & Rationale

- Epidemiologic studies report that Gulf War Illness (GWI) criteria are met in 45% to 60% of military personnel returning from combat. (Fukuda et al, 1998; Baker et al, 1997, Wolfe et al, 2002)
- Patients with GWI may consume a disproportionate share of medical resources by virtue of their over-reliance on diagnostic testing and desire for palliative care. (Reid et al, 2002)
- With the recent deployment of troops to Iraq, an influx of veterans with unexplained symptoms may overwhelm the VA healthcare system.

Background & Rationale (cont'd)

- Written emotional disclosure (ED) reduces healthcare utilization in both healthy and medically ill individuals. (Greenberg et al., 1996; Pennebaker & Beall, 1986; Pennebaker et al., 1988; Tojek et al., 2003)
- No research has directly addressed the question of whether written ED delivered on-line can reduce the use of medical services in veterans with GWI
- No studies have attempted to identify the mediators of reduced utilization following ED.

Primary Aims

1) Conduct a randomized controlled trial that evaluates whether a written emotional disclosure intervention delivered via the Internet reduces health care utilization in veterans with GWI
2) Determine a possible mechanism (symptom attribution) underlying the efficacy of emotional disclosure

Experimental Plan

- Veterans will be randomly assigned to On-Line ED + WRIISC Care (N=65) or WRIISC Care Only (N=65)
- Both groups will receive assessment at baseline, 6 months, and 12 months
  - Utilization (chart review), symptom checklist, functional health status, illness attribution, satisfaction care, etc.
- On-Line ED group will receive three e-mails across 3 weeks with instructions to write about the most stressful event that they have experienced. (Pennebaker, 1988)

Implications

- If effective, On-Line ED provides an efficient and easily accessible treatment for geographically dispersed veterans with GWI.
- Potential treatment benefits include reduced overutilization of healthcare services, increased quality of life, and patient satisfaction.

Presentation 12 – Drew Helmer

Provider Effect on Outpatient Utilization in Veterans with Symptoms

Health Services Research Career Development Award

Drew A. Helmer, MD, MS

Goal

- Improve quality of care for veterans with deployment-related health concerns

Background

- Persian Gulf War Veterans report unexpectedly high rates of unexplained chronic pain and fatigue. Although difficult to address effectively, there are evidence-based recommendations for primary care providers. The quality of care of veterans with these conditions is anecdotally poor, but there is little evidence of this.

Method

- Assess current care for medically unexplained chronic pain and fatigue from the primary care provider and patient perspectives
  - Semi-structured interviews of PCPs
  - Chart review
  - Patient surveys
  - Claims data analysis
- Develop quality indicators for measuring performance
- Apply findings effectively and monitor change in outcomes

Funding

- **Dr. Helmer's salary covered by RCD**
- **Additional funding requested**
  - VISN 3 seed grant "Impact of implementation of a clinical practice guideline for medically unexplained chronic pain and fatigue on patient-provider communication"
  - PGW RFA "Evaluation of the Unexplained Pain & Fatigue Care Guideline for Veterans"
- **Infrastructure/Institutional Support**
  - WRIISC
  - Center for Health Care Knowledge Management
  - VA-NJHCS- Ambulatory Care

Presentation 13 – John Ottenweller

Proposal for Gulf War RFA and Deployment-Related REAP

Proposals discussed earlier

Copeland – "Process evaluation of the PTSD clinical practice guideline for veterans"

Ciccone – "Telemedicine treatment for veterans with Gulf War illness"

Process Evaluation of the PTSD clinical practice guideline for veterans

- Principal Investigator: H. Liesel Copeland
- Co-Investigators:
  - WRIISC: Drew Helmer
  - National Center for PTSD: Josef Ruzek
  - Washington DC VA: Robin Peck
  - Indianapolis VA: Matt Bair
  - Columbia MO VA: Ayyasamy Panneerselvam
- Proposal to Gulf War RFA

Rationale

- Gulf War veterans have a three-fold higher incidence of PTSD than veterans of the same era not deployed to the gulf. Prevalence is similar to Vietnam veterans.
- PTSD is under-recognized in primary care.
- The VA recently released an evidence-based clinical practice guideline for PTSD
- Adoption of the guideline could improve clinical care.
- There is a need to evaluate the extent of implementation (awareness and adoption) of the guideline in primary care settings

Specific Aims

- Elucidate primary care providers' knowledge, needs, attitudes, beliefs, and intentions about he CPG for PTSD
- Describe patients' responses to assessment of key components of the PTSD CPG
- Identify documentation of diagnosis and care of patients with PTSD in the medical records
- Compare the three perspectives (clinician, patient, chart documentation) of need and utility for the PTSD CPG

Data Collection

- Multi-method data collection with triangulation of sources
  - **Interviews of Primary Care providers**
    - Knowledge, perceptions, use
  - **Questionnaires of Primary Care providers**
    - Knowledge, perceptions, use
  - **Questionnaires of Patients**
    - Symptoms, provider communication, recall of screening
  - **Medical Record review**
    - Implementation – diagnosis, key guideline steps

On-Line Treatment for Veterans with War-Related Multisymptom Illness

Principal Investigator: Donald S. Ciccone, Ph.D.
Co-Investigator: Helena K. Chandler, Ph.D.

Background

- As far back as the American Civil War, soldiers have reported nonspecific ailments that could not be attributed to an underlying medical cause.
- The prevalence of GWI or similar symptom-based illness may be as high as 45% to 60% in deployed personnel. (Fukuda et al, 1998; Baker et al, 1997, Wolfe et al, 2002)

Background (continued)

- Despite an uncertain etiology, GWI and other symptom-based ailments have substantial consequences for veteran health:
- Frequent VA medical visitation
- Physical disability
- Psychological distress/psychiatric morbidity.

Study Rationale

- In order to address the anticipated increase in GWI, new and more efficient treatments are urgently needed to augment or replace standard VA care.

Rationale for Telemedicine

- Fortunately, an effective treatment using cognitive-behavioral techniques (CBT) has been developed to ameliorate symptom-related distress and reduce unnecessary healthcare utilization.
- Despite evidence of CBT efficacy provided by RCTs, a major limitation is that patients are often nonadherent. Only 38% were adherent in a recent large scale trial of CBT.
- Clinical effectiveness of CBT is undermined if fewer than half of those who need treatment are likely to attend.

A Randomized Trial of Telemedicine

- The proposed study will address this public health problem by testing a novel treatment for GWI-On-Line CBT using instant voice messaging (voice stream technology).
- Treatment is administered over the Internet and allows veterans to speak with CBT practitioners in real time just as they would on the telephone.

Study Aims

Aim 1. Determine the efficacy of On-Line CBT for veterans with GWI who are frequent consumers of ambulatory medical care.

Aim 2. Determine whether CBT for veterans with GWI leads to a reduction in the cost of VA healthcare

Study Design

150 High utilizing veterans will be assigned to one of three study conditions:

I On- Line CBT + Customary Medical Care (N=50)

II In-Person CBT + Customary Medical Care (N=50)

III Customary Medical Care Only (N=50)

Study Design

•Intent-To-Treat Strategy

•Primary Outcome: Utilization of VA medical services

•Assessment Protocol: Electronic chart review 1 yr before and 1 yr after treatment

VA Significance

•The proposed study is intended to reduce unnecessary VA utilization while preserving or improving physical function, patient satisfaction and other quality of life indicators.

•Treatment can be made readily available to veterans regardless of their geographic location.

Long Term VA Benefits

Long-term benefits may also include:

•Lower costs for medical care

•Improved allocation of VA resources

•Improved quality of life for GWI veterans

•Less psychiatric morbidity

•Lower risk of iatrogenic injury.

Proposals from Other Investigators

Kevin Beck, PhD – "Interoceptive stressor conditioning: a model for Gulf War Illness"

Shelley Weaver, PhD – "Early life determinants of vulnerability to pyridostigmine bromide"

Cytokine Levels in Gulf War Veterans, their Spouses and Era Veterans

Principal Investigator:

John Ottenweller

Co-Investigators:

Clare Mahan

Joel Karlinsky

Nicholas Ponzio and William Gause

Rosemary Toomey

Key Questions

Do GVs show signs of immune activation compared with NGVs or civilians?

Do they show a shift to a Th2 pattern?

Are plasma cytokine levels associated with specific diseases, symptoms, signs or disabilities in GVs?

Are plasma cytokine levels associated with specific exposures in the Gulf, particularly vaccines?

Preliminary Results

Both Mark Peakman and I presented evidence of immune dysfunction in sick GVs at the last meeting of your committee.

Our group has reported evidence of persistent immune activation in GVs that is associated with cognitive impairments and lower levels of physical functioning.

Experimental Plan

Plasma levels of ten cytokines (IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12, IL-13, IFN-γ and TNF-α) will be measured in about 1,000 GVs, 1,000 NGVs and 1,000 spouses of these veterans who participated in Phase III of the NHS.

Multivariate statistical models will corporate other data from Phases I/II (e.g., demographics, military conditions, environmental exposures, vaccinations) and Phase III (e.g., medical conditions, illness characteristics, cognitive function, cortisol levels, functional status) of the NHS.

We will determine the demographic, military characteristics and Gulf exposures (including vaccines) that are associated with cytokines levels.

We will determine whether cytokine levels along with other variables are associated with specific diseases, health outcomes or functional outcomes in GVs.

We will determine whether these associations are unique to GVs or whether they also occur in NGVs or civilians.

Multidimensional Predictors and Outcomes of Unexplained Gulf War Illness

Principal Investigator: John Ottenweller

Co-Investigators:

NJ WRIISC:
Benjamin Natelson,
Donald Ciccone
Usha Sambamoorthi

Hines CSP:
Domenic Reda
Kwan Hur
Renee Alpern

DC WRIISC:
Clare Mahan

St. Louis VA:
Seth Eisen
Melvin Blanchard

Harvard:
Rosemary Toomey

Rationale

Analysis of NHS data has so far been divided into niches that looked at a limited number of variables in one domain.

There needs to be a broader, overall analysis that incorporates all the information collected in the NHS.

However, funding has essentially run out for further analyses of NHS data.

Key Questions

Are there subgroups of sick GVs with distinctive illness patterns?

Are there subgroups of sick GVs with different outcomes, i.e. different patterns in their functional impairments?

Can GVs be subdivided into groups based on the different health consequences of their illness?

Can either the illness subgroups or outcomes be related to specific military conditions or exposures in the Gulf?

Analytic Design

Data from all three phases of the NHS will be merged with physiological data and maybe immune data.

Factor analysis will be performed on 10 domains in these data: demographic/deployment, general physical health, neurologic, dermatologic, laboratory chemistry, psychological/cognitive, fatigue, pain, immune and quality of life.

The primary outcomes will come from factors derived from the quality of life domain.

Data from the other domains (except the demographic domain) will be used to define characteristics of illness subgroups (current manifestations of illness) and the consequences of these illnesses.

Multivariate regression models will be used to see whether different outcomes can be associated with illness subgroups, different consequences of illness, or demographic and military antecedents.

Research Center for Deployment-Related Illnesses

Principal Investigator: Thomas W. Findley, M.D., Ph.D.

Co-Director: John E. Ottenweller, Ph.D.

Other Participants: WRIISC Faculty

Background

The Research Enhance Award Program (REAP) provides infrastructure support and funds for pilot experiments to groups of VA-funded researchers at one site working on the same problem.

REAPs are generally funded at $250,000/yr with $100,000 for Equipment

Call for Proposals listed "Gulf War Illnesses" and "Deployment-Related Conditions" as areas of interest for new REAPs

- But included "other collaborative initiatives … with relevancy to veterans health"

Our application on July 1 will be competing with 32 currently funded REAPs on Cancer, Diabetes, Neurodegenerative Diseases and Molecular Medicine, etc.

Plan for NJ REAP on Deployment-Related Illnesses

Multidisciplinary Approach to Studies

MDs:

- Physiatry, Neurology, Internal Medicine, Occupational Medicine, Pulmonology, Endocrinology and Infectious Diseases

PhDs:

- Neuroscience, Neuroendocrinology, Psychology, Functional Imaging, Exercise Science, Pain, Statistics, Public Health and Health Economics

Research Focus

Improving Clinical Research on Gulf War Illnesses and Deployment Health Problems

Hyporeactivity to stimuli may be a general problem in unexplained deployment-related illnesses.

Clinical trials in those with unexplained illnesses present particular challenges.

Overall Research Plan

Stress reactivity and other measures will be assessed before and after two treatment arms

- One-on-One Cognitive Behavioral Therapy
- Individualized Exercise Therapy

Pilot 1: Acute Stress Reactivity in Gulf War Veterans with CMI

Key Questions:

- Does the hyporeactivity we have seen so far extend to other stimuli and responses?
- Are there subgroups that respond differently to physical and psychological stressors?
  - Both in the stressors they respond to and the stress systems that react to the stressors
- How is reactivity in the various stress response systems related?

Protocol

Veterans with unexplained CMI and healthy controls will be exposed to 3 stressors:

- Physical Stressor - Maximal Exercise Test
- Psychological Stressors - Mental Arithmetic and Speech Task

Stress Response Systems:

- Hormones, Cardiovascular, Respiratory, Metabolic

Other Variables:

- Psychiatric Conditions, Cognitive Performance, Balance, Sensory Testing, Activity Levels

Analytic Plan

Compare responses of those with and without Axis I psychopathology

Determine whether there are predictors that can separate high and low responders to each stressor

Determine the relationships between the magnitudes of the responses in the different stress systems

The results from Pilot I will be used as pre-measures for treatment trials.

In addition, we will collect data using validated questionnaires for depression, anxiety, physical health, coping, functional status, fatigue, pain, activities of daily living and quality of life.

Pilot 2: Cognitive Behavioral Therapy of Gulf Veterans with CMI

CBT proved somewhat effective in VA trial

- But there was very poor compliance and the group CBT used was not the best protocol

Pilot will determine if delivering CBT over the telephone will be improve compliance and health, decrease healthcare utilization, and alter psychological and physiological measures.

- First use of laboratory measures in such a trial

Protocol

90 GVs with CMI will go through the protocol for Pilot I.

60 will be randomly assigned to the CBT group
30 will served as ordinary care controls

One hour weekly CBT sessions for10 weeks

- Treatment manuals based on "Personal Health Improvement Program" and modifications to protocol used in VA trial.

Pre-treatment measures repeated 6, 12 and 24 months after end of treatment. Other questionnaires include patient satisfaction survey and coping skills questionnaire.

Chart abstraction used to determine healthcare utilization over 24 months and cost effectiveness.

Pilot 3: An Individualized Exercise Prescription for the Treatment of Gulf War Illnesses

Compliance with the exercise protocol in the VA trial was also very poor. And exercise was ineffective.

Compliance should be better when exercise prescription is individualized to each veteran's needs and capabilities.

Protocol

90 GVs with CMI will go through protocol for Pilot I.

60 will be randomly assigned to Exercise Group
30 will be randomly assigned to Standard Care

Evaluation of each subject's endurance, strength and flexibility

Devise an individualized 12 weeks exercise program that addresses specific areas of weaknesses for each veteran.

Post-treatment measures at 6, 12 and 24 months

Measures of exercise capacity, stress reactivity, balance and cognition provide objective measures of improvement

Exercise Treatment

Based on gradual progression in the frequency, intensity and duration of exercises.

Exercises to deal with cardiorespiratory fitness, muscle strength and endurance, functional movement and flexibility

Compliance will be monitored with weekly phone calls and an "ecological momentary assessment" watch that records activity levels and exercises.

Additional measure will be the Occupational and Leisure Time Physical Activity Questionnaires

Advantages of Combined Pilots

Same measures in Pilot 1 on 180 veterans with CMI to provide power for its analyses

Evaluate which measures in battery of tests are best for assessing improvement in trials

Objective biobehavioral measures of improvement

Can evaluate whether variables from Pilot 1 can predict who will benefit from CBT or Exercise

REAP Training Mission

It is expected that some REAP funds be used to hire and train fellows, but that cuts into pilot funds.

Applied for VA Clinical Research Center of Excellence to prepare young physicians for studying deployment-related health problems.

Size of program cut. We did very well, but not funded.

We have been awarded a **Special Fellowship Program** in Deployment Related Illnesses that will provide 2 slots for 5 years. For training clinicians to care for Gulf veterans and to do deployment-related health research

First fellow is MD/PhD physiatrist starting 7/1
Second fellow is clinical psychologist starting 9/1

Clinical Databases and Computer Guided Workup for Gulf Veterans

WRIISC Clinicians have developed a standardized intake protocol we will share with DC WRIISC.

We are implementing secure databases to store the same clinical data at the two WRIISCs so they can be merged for research purposes.

We are developing a computer interface for both clinicians and veterans to input data that will be stand alone and could be used anywhere.

Ultimate goal is combine this software with the VA/DOD Clinical Practice Guidelines for Post-Deployment Illnesses to produce computerized aide for evaluating Gulf Veterans.

Future Directions for Gulf War Research

Clinical Research

- Multidisciplinary research projects and teams
  - Identifying subgroups of GVs with distinctive problems
  - Comorbid physical and psychological conditions
  - Brain Imaging for neurologic problems
  - Animal Studies on subclinical neurotoxicity
  - Implementation Research - education of VA clinicians
  - Risk Perception/Communication for Military/Veterans

Small Clinical Trials

Subgroups that may respond differently
Better outcome measures
Improving compliance

CBT – which components work
Exercise – which components work
Low-dose cortisol

Presentation 14 – Drew Helmer

WRIISC Clinical Program

Prior Conflict Evaluations

Goal

- To provide a comprehensive, multidisciplinary clinical evaluation of veterans with medically unexplained, debilitating deployment-related health problems

Referral Process

- Routed through Environmental Agents Service in VA Central Office
- Require referral from VHA primary care provider
- Home VA Medical Center pays half of travel expense

Screening

- Three exclusion criteria (delay evaluation)
  - Substance abuse (untreated) in past 6 months
  - Unsafe to travel
  - Homeless
- Review VHA and other medical records
  - Work with referring PCP to complete work up of medically unexplained symptoms

Numbers/Access

- 700,000 US troops deployed to PG
- 80,000 evaluated through VA or DoD registries
- 100 referred to WRIISC through VACO or local template
- 52 evaluated

Demographic Characteristics

- Gender
- Age
- Deployment
- Branch
- Component
- Referred by VACO

Clinical Characteristics

- Functional Status/Quality of Life
- Symptoms
- Diagnoses
- Disability/service connection

Exposure Concerns

- Reported
- Most common specific-concerns

Follow up/Satisfaction

- Exit interview
- Comprehensive Summary
- 3 week follow up phone call
- 6 month follow up survey

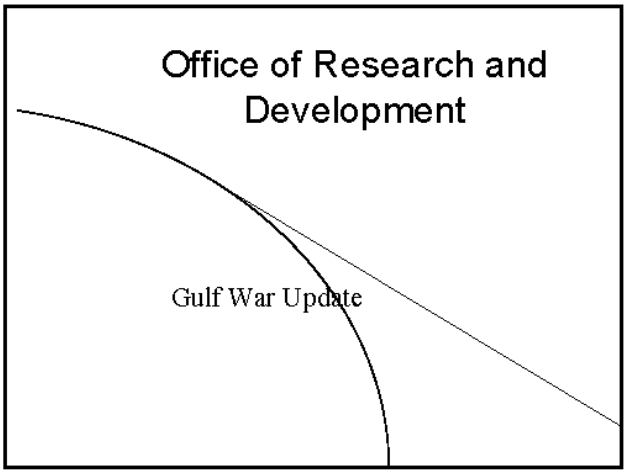
Summary of Experience

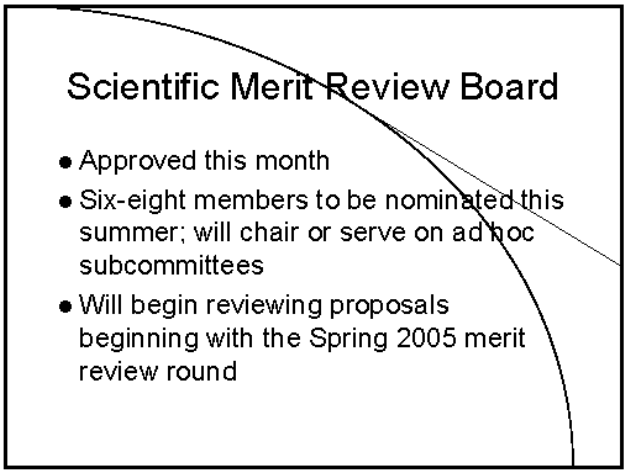
- Multidisciplinary evaluation works
  - Patient feedback
  - PCP feedback
  - New diagnoses/treatment recommendations
- Access is a problem
  - "There is no such thing as a war-related illness center."

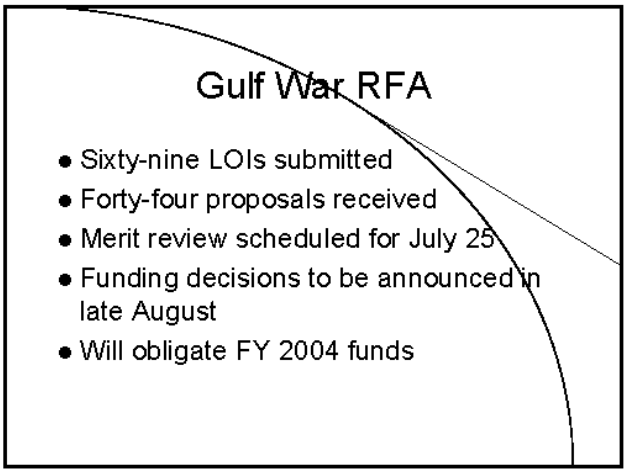
Future Directions

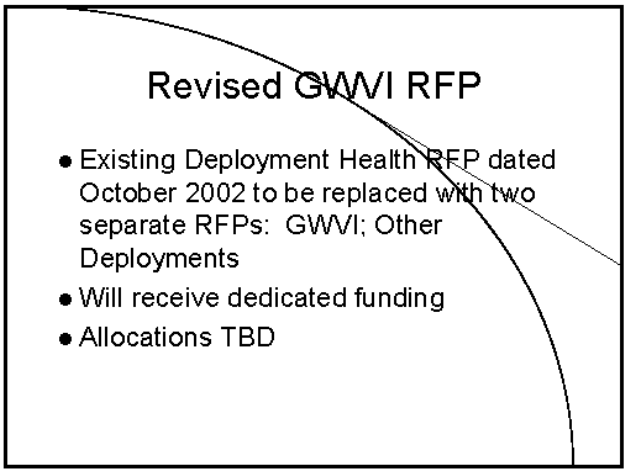
- Disseminate WRIISC program approach appropriately to VHA PCP's
  - Provider education
  - Patient education
- Improve access for veterans, especially PGW veterans

Presentation 15 – Roger Kaplan









War-Related Illness and Injury Study Center

- Action Office: Office of Public Health and Environmental Hazards
- Proposal submitted to Deputy Under Secretary for Review
- Preference will be given to proposals originating from facilities located in other regions of the US

War-Related Illness and Injury Study Center

- Proposals must focus on:
  - Unique health problems of Gulf War veterans
  - Neurological diseases
  - New treatment modalities
  - Unique health problems of women veterans

Recently Approved Drug Trial

- ALS treatment trial using sodium phenyl butyrate (NaPB)
  - NaPB increased survivability in ALS mice
  - Study will begin with a Phase I trial to determine tolerability in patients
  - Phase II trial to be conducted at multiple sites

Presentation 16- John Concato

ACETYLCHOLINESTERASE ACTIVITY IN GULF WAR DEPLOYED AND ERA VETERANS: JUN '04 UPDATE

John Concato, M.D., M.S., M.P.H.

West Haven Clinical Epidemiology Research Center (CERC)

BACKGROUND

Original proposal (B. Doebbeling, H. Soreq):
Research study to determine whether mood or anxiety disorders are related to serum levels of various enzymes among Persian Gulf veterans

Completed and ongoing analyses (West Haven CERC):
Based on original and additional "exploratory" hypotheses

SOURCES OF DATA

Questionnaire responses from Iowa Gulf War Cohort Study
- Wave I: 3,695 veterans of Persian Gulf era, from Iowa
- Wave II: 374 case patients with cognitive dysfunction, depression, or chronic widespread pain; 228 controls without these conditions (N=602 subset of Wave I)

Laboratory analyses of stored sera, at Hebrew University
- Acetylcholinesterase (AChE)
- Butyrylcholinesterase (BChE)
- Paraoxonase, Arylesterase (PON1, Aryl)

FINAL STUDY SAMPLE FOR CURRENT ANALYSES

Wave II participants:		602
• enzymes not measured	- 25	
Full study cohort:		577
• non-white or female veterans	- 89	
Final study cohort:		488

ORIGINAL HYPOTHESES

1. Mood and anxiety symptoms are associated with selected blood enzyme levels
2. Deployed (vs. non-deployed) Gulf War veterans have lower capacity to increase blood AChE levels
3. Veterans with (vs. without) symptoms of Gulf War Veterans Illness (GWVI) have lower capacity to increase blood AChE levels under challenge

INTERIM SUMMARY

1. Findings not consistent with original hypotheses regarding association of anxiety or mood disorders and AChE or other enzyme levels in this population
2. Deployment status not associated with AChE or other enzyme levels
3. Symptoms of GWVI were not strongly associated with AChE or other enzyme levels

ADDITIONAL "CANDIDATE" ANALYSES

1. Immunoassays for splice variant of AChE [AChE-R]

ADDITIONAL "CANDIDATE" ANALYSES

1. Immunoassays for splice variant of AChE [AChE-R]:
   - not yet done, based on results of planned analyses

ANALYSIS OF ACHE-R

Original protocol: *If blinded testing of serum identifies a significant decrease in total AChE activity on the basis of mood and anxiety symptoms, immunoassays for the level of the "readthrough" splice variant of acetylcholinesterase will be conducted.* [No association found]

Revised hypotheses under discussion: approval for analyses given

ADDITIONAL "CANDIDATE" ANALYSES

1. Immunoassays for splice variant of AChE [AChE-R]:
   - not yet done, based on results of planned analyses

2. Comparison of enzyme activity among veterans vs. available database of U.S. adults

ADDITIONAL "CANDIDATE" ANALYSES

1. Immunoassays for splice variant of AChE [AChE-R]:
   - not yet done, based on results of planned analyses

2. Comparison of enzyme activity among veterans vs. available database of U.S. adults:
   - methodological issues re: sampling, clustering, covariates

COMPARISON TO "HEALTHY" POPULATION

Methodological problems related to:

- sampling differences (e.g., race, geographic location)
- clustering effects (e.g., siblings, offspring)
- covariates (e.g., age, body mass index, meds, acute illness)

Cogent hypothesis not yet developed

ADDITIONAL "CANDIDATE" ANALYSES

1. Immunoassays for splice variant of AChE [AChE-R]:
   - not yet done, based on results of planned analyses
2. Comparison of enzyme activity among veterans vs. available database of U.S. adults:
   - methodological issues re: sampling, clustering, covariates
3. Examination of self-reported exposures and enzyme levels

ADDITIONAL "CANDIDATE" ANALYSES

1. Immunoassays for splice variant of AChE [AChE-R]:
   - not yet done, based on results of planned analyses
2. Comparison of enzyme activity among veterans vs. available database of U.S. adults:
   - methodological issues re: sampling, clustering, covariates
3. Examination of self-reported exposures and enzyme levels:
   - results presented today

FORMAT FOR CURRENT ANALYSES

- Enzyme levels assigned as outcome variables in multiple linear regression analyses; results presented as difference in values (nmol/min/ml) for exposed vs. non-exposed
- Models done both unadjusted and adjusted for: age, BMI, smoking, acute illness, antidepressant medications, alcohol/drug use, case-control status in original Iowa study

DEMOGRAPHIC AND SERVICE CHARACTERISTICS
(N=577)

Age (± std dev)	mean 39 (± 9) yrs
Education ≥ some college	65%
Employed	90%
Married or living with partner	72%
Gulf Service	
• Regular military	32%
• Guard/Reserve	68%
• Deployed	72%

[87% male; 97% white]

OTHER CHARACTERISTICS
(N=577)

Hypertension	13%
Coronary artery disease	2%
Drug abuse/dependence	2%
Alcohol abuse/dependence	6%
Antidepressant use	9%
Antipsychotic use	<1%
Post-traumatic stress disorder:	
• deployed	9%
• non-deployed	3%

OVERALL RESULTS FOR ENZYME LEVELS
(NMOL/MIN/ML; N=577 FULL COHORT)

Enzyme	Range	Median	Mean ± sd
AChE	130-2908	839	882 ± 362
BChE	142-11412	5053	5065 ± 1476
PON	3-185	38	43 ± 25
ARYL	0-46	18	17 ± 7

SELF-REPORTED EXPOSURES AMONG DEPLOYED
(N=414)

Est. mean (std dev) days in Gulf	154 (±77)
Vaccinations	11 (±19)
Pyridostigmine tabs	25 (±69)
Chemical attack alert	81%
Chemical warfare agents	8%
• nerve gas	9%
• mustard gas/blistering agent	3%
Pesticides	63%
• personal creams, etc.	60%
• clothing or bedding	36%

SELF-REPORTED EXPOSURES AMONG DEPLOYED
(N=414)

Petrochemicals/solvents	93%
Smoke/combustion products	95%
Sources of infectious agents	91%
Sources of lead from fuels	88%
Ionizing/non-ionizing radiation	23%
Physical trauma	6%
Heat stress	23%
Psychological stressors	35%

[OTHER TABLE AND FIGURES BEING CHECKED

PRIOR TO PUBLICATION]

SUMMARY AND CONCLUSIONS

Most self-reported exposures (vs. non-exposures) not associated with difference in enzyme levels

Given multiple comparisons and other methodological issues, limited evidence exists re: associations (e.g., petrochemicals and PON)

Results can help inform future proposals and protocols

Presentation 17 – Beatrice Golomb

June 2004 Review of Recent Gulf War Research

Beatrice A. Golomb, MD, PhD

R 1

Epidemiology

R 2

Smith 2004: Registries vs Hospitalizations

Question: Is Gulf War registry participation a marker of worse health -- by the objective outcome of hospitalizations

Subject:All US GWV in DoD registry (N=69189) vs all GW-era deployed nonparticipants (N=477,333). Excludes Reserve, National Guard.

Method: Cox proportional hazards on hospitalizations from 8-1-91 to 6-1-94 = day before initiation of DoD registry

Analysis: Cox regression. Saturated and manual backward stepwise.

Covariates: demographics; exposures*, deployment

Exposures: Khamisyah plume; Ax/BT; oil fire plume. (PB, pesticides not assessed.)

Smith TC et al 2004 J Occup Env Medicine 46

R 3

Smith 2004: Registries vs Hospitalizations

Results: Risk Factors for Hospitalization

Factor	RR (95%CI)
Registry participant	**1.44 (1.40-1.46)**
Female	1.55 (1.51-1.59)
Age >31	1.12 (1.10-1.15)
Army vs Navy/CoastGd	1.36 (1.33-1.39)
Enlisted (vs officer)	1.50 (1.46-1.55)
Prewar hospitalization	1.66 (1.62-1.70)
BT vaccine	1.43 (1.12-1.82)
Healthcare worker	1.27 (1.23-1.31)

NS: Ax vax 1.03, .92-1.14, rel to not and unknown)

NS: Khamisiyah 0.99 (0.96-1.01)

R 4

Hotopf 2004: Predicting Persistent Illness in GWV

Question: What predicts persistent illness in GWV?

Subjects: UK GWV sampled stratified on fatigue: N = 511; 484; 250 with Chalder fatigue > 9, 4-8, <4

Design: Retrospective cohort: assess how baseline RF relate to persistent health outcomes

Outcomes: 1. Chalder fatigue; 2. GHQ-12 psych distress; 3. SF-36 phys functioning. BUT did not give results for phys functioning!

Covariates/ Factors assessed

- Model 1: Sociodemog: age, sex, rank, service, marital
- Model 2: Model 1 + severity of sx at baseline
- Model 3: Model 2 + tot exposures (0-29), tot vaccines, believe have GWS, case in GHQ-12

Analysis: Regression; then stepwise regression; then posthoc by RF

Hotopf M et al 2004. Psychological Med 34: 747-54.

R 5

Hotopf 2004: Predicting Persistent Illness in GWV

RF for remaining a "case" for that outcome

(Prev published RFs for being a case @ stage 2)

RF	Fatigue	GHQPsych
Age (yr)	NS	1.04*
Male	NS	2.0* (Male!)
Single	NS	NS
Army v Navy	2.7**	NS
Case@ stage 1	1.23**	1.12*
GHQ case	1.6*	(1.12*)
Self-report GWS	2.0**	1.8*
Total exposures	NS	NS
Vaccine quintile	NS	NS

Hotopf M et al 2004. Psychological Med 34: 747-54.

R 6

Hotopf 2004: Predicting Persistent Illness in GWV

Post-hoc analysis: Individual exposures associated c persistence. Among 29 exposures (not cited here), adjusted for demographics and stage 1 score. {Note: Some variables' contribution will be through their impact on stage 1 score}

RF	Fatigue	GHQPsych
Smoke from oil fires	1.3*	1.4*
Burning rubbish/feces	1.6*	1.4*
Chem agt-resistant paint	1.4*	NS
See dead animals	1.3*	NS
See burnt/disfigured peopl	1.3*	NS
Wear NBC suits (x training)	1.4*	NS
Hear chemical alarms	1.5*	NS
Paints & solvents	NS	1.4*
Consuming local food	NS	1.4*

Hotopf M et al 2004. Psychological Med 34: 747-54.

R 7

Birth Outcomes

R 8

Araneta 2004: US women veterans conception & pregnancy outcomes

Question: Do pregnancy outcomes differ in GW vs nondeployed women, who became pregnant during or after the war?

Subjects: From records from 153 military hospitals: women pregnant from 8-90 to 5-92 who were in GW deployed units, comparing GW deployed to nondeployed from same units.

-1558 pregnancy related admissions include:

- 415 GW exposed pregnancies;
- 298 GWV postwar conceptions (difference btn reported date of return & date of birth > reported gestational age)
- 427 NDV conceptions (in deployed unit but state never deployed).

Design: Postal survey in 1997 & 1998. Deployment date by data for unit. Deployment status by self-report (whether deployed).

Outcomes: Stillbirth. Spont abortion. Ectopic preg.

Analysis: Multivariate adjusted regression

R 9

Araneta 2004: US women veterans conception & pregnancy outcomes. Results

Stillbirths *lower* in deployed women unadjusted (2.3% vs 0.2%, 0.7%)

Adjusted Results*:	Spont ab	Ectopic preg
GW conception	1.45 (NS)	1.90 (NS)
GW postwar concepx	2.90 (1.86-4.53)	7.35 (2.97-18.2)

*Covariates: Age, race, educ, marital, rank, branch, parity, hx spont abortion, history of fetal los: demog from DMDC

*Compared to conceptions of nondeployed women from deployed units (ref group)

**Note: effects ~unchanged with adjustment*

Note: points out that misclassification may have been present for GW conception, since unit sent but some preg may have had deployment rescinded (deployment data by unit)

R 10

Araneta MR 2004. Ann Epidemiol 14: 109-116. DMDC = Defense Manpower Data Ctr

Doyle: UK Birth Outcomes

Question: Are Offspring of UK PGWV at incr risk of fetal death or malformation?

Ss: UK GWV vs "demographically similar" nondeployed era control group.

- 16442 male & 484 female UK PGWV (53% & 72% of questionnaires);
- 11,517 male & 377female era controls (42% & 60% of questionnaires).

Design: Retrospective cohort study, with repro hx by validated postal questionnaire btn 1998 and 2001.

Outcomes: Fetal death or malformation among 27959 pregnancies by men and 861 pregnancies by women conceived between GW1 and Nov 1997.

Death:

- Early miscarriage: < 12 weeks
- Late miscarriage: 12-23 weeks
- Stillbirth: ≥23 weeks
- Exclude: Ectopic pregnancies, terminations*

Malformation: diagnosed in utero, at birth, or any time after birth

- Coding by info from clinician wher available, otherwise by parent description
- Double count anomalies if in more than one group (just once if multiple, same group)
- Exclude: minor anomalies

R 11

Doyle: UK Birth Outcomes

Analysis: logistic regression, adjusted

Unit of analysis: pregnancy for a miscarriage; fetus/infant for stillbirth or malformation

Covariates adjusted:

- Year of pregnancy end; pregnancy order for that parent; age of mother; service; rank (All analyses)
- Previous fetal death; analysis of late miscarriage/stillbirth/congen malformation for multiplicity. (Fetal death analyses) (None changed estimate by > 1-2%).

Comparator groups:

- Nuclear Industry Family Study
- England & Wales Annual registered stillbirths by maternal age for

Doyle P 2004. Int J Epi 33: 74-6

R 12

Doyle: UK Birth Outcomes

	Fetal death	fetal death		Stillbirth
MEN	<12wk	12-23wk	all	
All pregnancies since PGW	1.5 (1.3,1.6)	1.2 (1.1,1.3)	1.4 (1.3,1.5)	0.9 (.7,1.3)
All 1st pregnancy since PGW	1.5 (1.4,1.7)	1.2 (1.0,1.3)	1.4 (1.3,1.5)	0.9 (.6,1.4)
1st preg p PGW, conc'd '90-'91	1.5 (1.2,1.9)	1.2 (0.9,1.7)	1.4 (1.2,1.7)	1.9 (.7,5.1)
WOMEN				
All pregnancies since PGW	1.0	0.8	1.0	2.0 (.3,15)
All 1st pregnancy since PGW	1.4 (0.8,2.5)	-0.7 (0.3,1.7)	1.2 (0.7,1.9)	∞

VS NIFS COMPARATOR GROUP

-GWV not different from comparator groups, BUT:

-NDV fetal loss low: 30%↓ early fetal death (p = 0.004); 40% ↓ late fetal death (p=0.001)

- No diff in stillbirths NDV or GWV (and no dif vs England & Wales stillbirths)

Doyle P 2004. Int J Epi 33: 74-6

R 13

Doyle: UK Birth Outcomes: Self-report

Malformation	Adjusted OR
MEN (selected, significant or strong)	
Any	1.5 (1.3-1.7)
CNS	1.4 (0.9-2.3)
Genital	1.8 (1.0-3.0)
Urinary	1.6 (1.1-2.3)
- Renal	1.6 (1.0-2.7)
- Urinary tract	1.6 (1.0-2.4)
Musculoskeletal	1.8 (1.3-2.4)
- Other musculoskeletal	1.4 (1.0-2.1)
Other nonchromosomal	1.7 (1.0-3.0)
- Non-specified nonc'somal	3.5 (1.5-8.4)
Cranial neural crest	1.3 (1.0-1.7)
Metabolic & Single Gene defect	2.0 (0.9., 4.8)
WOMEN (all were nonsignificant)	
Any	1.7 (0.7-3.9)
C'somal	3.1 (0.3, 29.9)

R 14

Doyle: UK Birth Outcomes: Clinically Confirmed

Clinically confirmed Male birth outcomes: N = 330 GWV/ 196 NDV

(vs Self-report, prior page

Malformation	Adjusted OR
Any	1.3 (1.0-1.5)
Urinary	1.6 (1.0-2.5)
Musculoskeletal	1.5 (1.0-2.2)
- Other musculoskeletal	2.0 (1.0-4.1)

Note: OR show trend or effect of increase in 23 conditions, trend to decrease in 8. This is significantly different than expected by chance

Doyle P 2004. Int J Epi 33: 74-6

R 15

Objective Markers in III PGWV

R 16

Hippocampal Cell Loss by proton MR Spect

Question: Is there evidence of hippocampal neuron loss in ill PGWV?

Comment: The HC (hippocampus) is important in acquiring new memories.

Previous work by Sapolsky has shown that HC neuron loss occurs when energy demand exceeds supply AND there is stress.

Subjects: 10 ill PGWV. 5 well PGWV. 6 Vietnam veterans.

Outcome: NAA/Creatine ratio in HC (thought to signify neuron loss). Choline:creatine ratio comparing ill PGWV to controls.

ALSO: compare NAA:creatine in younger, age < median 44.2, vs older ∀

Result:

- NAA/Creatine ratio is significantly lower in ill GWV than either whole control group (p < 0.0057) or well PGWV controls (p =0.04)

- Younger group (< median -- all GWV) had lower value than older group; though neuron loss normally expected with age.

Menon PM 2004. Brain Res 1009: 189-194.

R 17

Cellular and Humoral Immune Abnormalities

Question: Do symptomatic PGWV have immune abnormalities?

Subjects: Delivered by R. Haines of U S Army req testing of 10th Army Unit GWV with sx. No medical records or health histories were forwarded.

Cases: 100 "symptomatic" GWV (no case def -- but reportedly with "common symptoms (joint pain, fatigue, headache, memory or concentration difficulties, sleep disturbance, and rash);

Controls: 100, including 50 asymptomatic vaccinated nondeployed & 50 healthy asymptomatic subjects for annual checkup. "Matched" on age & sex

Outcomes: CBC, chem, lipids, LFTs, T3, T4, TSH, AHA, RF, total IgA/IgG/IgM. Lc subset enumeration. NK cell cytotox assay. Lc mitogen assay. Myelin basic protein antibody. Striated & smooth muscle antibody. Immune complexes (IgG, IgM, IgA). Antibodies to EBV, CMV, HSV-1, HSV-2, HHV-6, VZV by ELISA.

Analysis: t-test of difference in mean. % outside expected range in cases vs controls

Vojdani & Thrasher. Environ Health Perspec 112: 840-846.

R 18

Cellular and Humoral Immune Abnormalities

Results	Patients vs controls	Comparison	p
CD3 T-cells	↑ct: 30% vs 5% had >79%	↑% outside expected range	< 0.05
CD-19 B cells	↑ct: 16 vs 11	% B cells	<0.001
CD4:CD8 ratio	↑ct: ratio 2.2 vs 1.3	% outside expected range	< 0.001
NK lytic activity	↓ct: 25 vs 37 lytic units	% with < 20 lytic units	< 0.01
Lc Mitogen stim*	PHA: GW > ctrl	stim index < 75% expected	< 0.01
		stim index > 125% expected	< 0.05
	PWM:	stim index < 75%	< 0.01
		stim index > 125% expected	NS
Autoantibodies	↑ct: 46 vs 28 mean igM	Mean ELISA units, IgM	< 0.001
		% with > 50 ELISA units	< 0.001
Abs to muscle	↑ct: 43 vs 16, IgG titers	IgG abs to smooth & striated mus	< 0.001
Immune complexes	↑ct: 51vs 35mEq/ml	Mean	< 0.001
		% with > 50mEq/L	< 0.01
Antibodies to viruses	Higher for each	Mean ELISA units (IgM, IgG)	< 0.001

∴ *Sometimes mean not different, but distribution is -- with more out of range at both ends

PHA = phytohemagglutinin. PWM = pokeweed mitogen.

Vojdani & Thrasher. Environ Health Perspec 112: 840-846.

R 19

More immune changes: Cytokine profiles

Question: Are there changes in cytokine, esp Th1/Th2 balance

Ss: UK symptomatic sGWV (40); well wGWV (80); sympt. Bosnia (20); sympt. Era (39)

Determination of "symptomatic" status: SF-36 phys fc < 72.2 (bottom decile)

Design: nested case-control study (drawn from UK sample)

Outcome: Cytokine profiles.

Results: Mixed Th0 pattern of immune system activation

Marker in sGWV	vs well GWV	vs sBEV*
Nonstimulated:		
IL4 ↑ (Th2)	< 0.05	<0.001
IL2 ↑ (Th1)	< 0.01	<0.001
IFN-gamma ↑ (Th1)	NS	< 0.05
Stimulated:		
IL10 ↑ (Tr)	< 0.0001	= 0.05

After control for age, gender, vaccination srtatus, antidepressant use, depressed mood, hx of atopic illness (some of which are outcomes & not *necessarily* appropriate to adjust), retain assoc of IL-2 and IFN-gamma, but not IL-4

*BEV = Bosnia & Era veterans

Skowera A et al 2004. J Clin Immunol 224: 66-73

R 20

More immune changes: Cytokine profiles

			Mean difference (95% CI)	
Index	SGWV	wGWV	Age/Gender	Age, Gender, Vacc, BDI, antidepressnt, hx atopy
Nonstimulated				
IL-4 (Th2)	2.98	2.4	0.04	0.33
IL-10 (Tr)	1.70	1.63	0.6	0.5
IFN-gamma (Th1)	1.85	1.39	0.03*	0.01*
IL-2 (Th1)	1.59	1.11	0.008*	0.001*
Stimulated (Polyclonally activated)				
IL-4 (Th2)	4.33	3.93	0.3	0.4
IL-10 (Tr)	5.08	3.20	<0.001*	<0.001*
IFN-gamma (Th1)	12.0	11.6	0.6	0.14
IL-2 (Th1)	18.4	16.4	0.4	0.2

∴ There are immune differences. Some show only under challenge conditions.
Skowera A et al 2004. J Clin Immunol 224: 66-73.

R 21

Squalene Antibodies

Question: Are there squalene abs in human serum and plasma?

Method: Adapt method to measure squalene abs from animals to humans. Test IgG and IgM.

Subjects: 3 human cohorts

A. 40: USAMRIID retirees: mean age 68 (most vaccinated)

B. 372: Frederick, MD: "Normal popn mean age 67 (most not vaccinated)

C. 299: Ft. Knox KY: Camp Memorial Blood Center, US Army Medical Departkment Activities (no addl info available)

USAMRIID = US Armacy Medical Research Institute of Infectious Diseases
Matyas G R et al 2004 J Immunological Methods 286:47-67

R 22

Squalene Antibodies

			Squalene Abs	
Cohort	AVA?	Age	IgG	IgM
US AMRIID	Most	68 (58-82)	7.5%	38%
Frederick	most not	67 (54-97)	15%	32%
Camp Memorial	presume not	Unknown	0%	19%
Difference			p<0.0001	p=0.0002

USAMRIID = US Armacy Medical Research Institute of Infectious Diseases
Matyas G R et al 2004 J Immunological Methods 286:47-67

R 23

Squalene Antibodies

Conclusion: Squalene abs are not rare; & not assoc with AVA (by this assay)

Support for safety of squalene adjuvants:

SQE-containing emulsion as part of flu vaccine licensed in Italy "has been given without adverse effects to hundreds of thousands of people"

"Numerous other clinical trials for influenza [and other] have used SQE emulsions. Vaccine reactions were typically mild. However, some moderate to severe reactions, which can be attributed to other adjuvants in the formulations, were reported."

Problem:

-Without active surveillance it was also thought AVA didn't have problems

-Attribution to other adjuvants is problematic; oil based adjuvants are unapproved in the US for a reason

-Did not assess relation of squalene abs to health

R 24

Squalene Antibodies

Issues:

- Cross reactivity of the assay?

-Age-relevant rates? Low rate in blood samples suggests may be low in younger age; relation to health not known BUT can't r/o contribution to health problems in the older population

-AVA recipients will have gotten AVA prior to 1990 inoculation program -- so comparability to age matched controls is of uncertain relevance

Matyas GR et al 2004 J Immunological Methods 286:47-67

R 25

Squalene Antibodies

Remaining Concerns:

It remains unconfirmed & unrepudiated whether squalene abs are more common in AVA recipients; or in ill PGWV.

It is unknown if there is a relation of squalene abs to health outcomes in the group studied

These authors own data from animals show that chol-abs have health consequences: *a fortiori* this could be expected for squalene abs

Additional study remains needed.

Matyas GR et al 2004 J Immunological Methods 286:47-67

R 26

Immune Effects of AChEi and chemical mixtures: Animal Studies

R 27

PB alters immune function in mice

- Subjects: Adult 7-8wk female B6C3F1 mice: 6-7 per group
- PB dosing/route/duration: 0, 1, 5, 10 or 20mg/kg/d po for 14 days 0 = distilled water control. (GW dose ~1.3mg/kg for 70kg man) Dose did not cause acute symptoms. The 1mg/kg/d PB dose did not alter BChE or AChE activity in mice
- Time to assessment:After the 14 ds (persistence not assessed)
- Outcomes: lymphoproliferation NK cell activity, SRBC-specific antibody plaque forming cell response, thymus and spleen weight and cellularity, thymic and splenic CD4:CD8 Lc populations
- No effect: spleen/thymus weight; spleen cellularity; Lc prolif resps; NK cell activity, wbc count, differential, RBC indices
- Hi dose effect: ↓ thymus cellularity, ↓ CD4:CD8, ↓ CD4-/CD8- cell types (20mg/kg/d; and in last case 10mg/kg/d)
- Lo dose effect: ↓ 1° IgM ab response to T-cell dependent antigen (includes 1mg/kg/d dose) (Humoral immunity)
- Peden-Adams MM et al 2004. Immunopharmacology and Immunotoxicology; 26:1-15. Pyridostigmine Bromide (PYR) alters

R 28

PB ↓ IgM abs in rats (humoral immunity)

- Conclusion: "It is clear that PYR suppresses humoral immunity... at treatment levels comparable to doses reported for military personnel"
- Comment: cite convergent evidence: also ↓ humoral immunity (SRBC-specific IgM production) by some other carbamates (ethylcarbamate; carbofuran), but reportedly not another (methyl carbamate).
- Some variability issues
- Aldicarb also ↓ ab production by one study, not another
- Depends on route of exposure? -- inhale carbaryl -> Response; oral/dermal -> no rsponse.
- Question: if there is short-term suppression, is there long-term upregulation (or suppression, or nothing) of ab production?

• Peden-Adams MM et al 2004. Immunopharmacology and Immunotoxicology 26: 1-15. Pyridostigmine bromide (PYR) alters immune function in B6C3F1 mice

R 29

Single or repeated low-level sarin on immune functions of inbred BALB/c mice)

•Subjects: Balb/C mice

•Exposure: sarin @ asymptomatic dose, 0.8µg/L in inhalation chamber, till 20-30% AChE inhibition. Vs air

•Timing of assessment: 1 week later

•Outcomes: Many in lungs, blood, spleen

•Findings: Indep of # exposures: ↓c CD3 cells in lungs. ↑ NK cell activity; ↓ lympoprolif & ↓ abil of paritoneal and alveolar macrophages to engulf microbes regardless of mitogen (former) or sarin concentration or # exposures.

•Depend on # exposures: N-oxide produx by peritoneal macrophages: ↓ after 1 exposure; vs ↑ after repeated low level exposures.

•Conclusion: Low level asympt sarin produces sustained changes in immune fcn even if single dose. Repeated doses may produce different effects

•Kanna J et al 2004. Basic and Clinical Pharmacol 94: 139-143. The influence of single or repeated low-level sarin exposure on immune functions of inbred BALB/c mice

R 30

Pesticide mixtures potentiate toxicity in murine thymocytes

Subjects: Mouse thymocytes (in vitro) from 8-12 week male C57BL/6 mice
Exposures: Lindane (L); malathion (M); permethrin (P) (separately or in mixtures of two)
Outcome:
-Apoptosis & necrotic cell death with 7-AAD staining

Result: More than additive:	**%apopt**	**%late apo/necro**
-L, M, both	**10,13,30**	**6,9,30**
-L, P, both	**8,13,17**	**9,16,36**

-P < 0.05 mixture vs sum of individual, all 4 cells

Olgun S et al 2004 Toxicology 196:181-195. Pesticide mixtures potentiate the toxicity in murine thymocytes

R 31

Question from Yesterday: Visceral Pain

R 32

Enhanced sensitivity to pain

Subjects: 12 GWV with abd pain & diarrhea s/p neg workup developed during PGW. 7 civilian & 5 veteran controls.

Exposure: a) rectal distension (35 & 55mm) & b) hot water R foot & hand (35° & 47°C x30sec)

Outcome: visual analog scale pain intensity & unpleasantness, 2 trials each

Finding: $p < 0.001$ higher rating of pain intensity and pain unpleasantness for both exposures

Conclusion: visceral hypersensitivity in PGWV with abd pain/diarrhea sim to that shown with irritable bowel. Also: cutaneous hypersensitivity "and higher levels of anxiety and somatic focus accounting for these differences in pain reporting" (no, attending them!)

Dunphy RC et al 2003, Pain 102: 79-85.

R 33

Backup Slide: Source of Information for Smith et al

R 34

Smith 2004: Registries vs Hospitalizations

Demographics: by Defense Manpower Data Center: gender, marital, age, race/ethnicity, home state, prewar hospitalization index from 7-31-89 to 8-1-90(the yr B4 war)

Exposures:

- Khamisiyah deployment (updated model);

- Oil well fire smoke from US Army Center for Health Promotion and Preventive Medicine with Natl Oceanic and Atmospheric Administration/Air Resources Lab estimate of 2hr unit exposures (meteorological and dispersion models overlayed onto troop location)

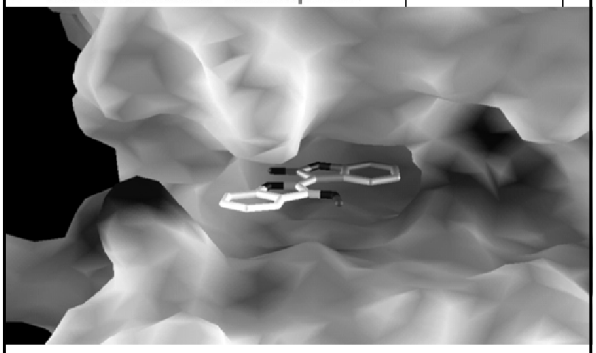
- Documented BT or anthrax vaccine

Deployment/Military: by Defense Manpower Data Center: Milit service branch, DoD occup specialty (of 10 major groups), milit pay grade, date of separation from milit, GW deployment hx, dates of entry and exit into theater

R 35

Presentation 18 – Allen Fienberg

Intra-Cellular Therapies



Research Advisory Committee on Gulf War Veterans' Illnesses
June 29th 2004

Neuronal Communication

- Nerve cells communicate by chemical neurotransmission; over 99% of all synapses in the brain use chemical neurotransmission
- There are two categories of neurotransmitters: 'fast neurotransmitters' and 'slow' neurotransmitters'

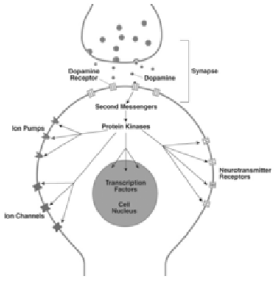
Intra-Cellular Therapies

Neuronal Communication (Cont'd)

- 'Fast' neurotransmitters control events occurring in the brain at 1/1,000 of a second
- 'Slow' neurotransmitters control events occurring in the brain over milliseconds to minutes

Intra-Cellular Therapies

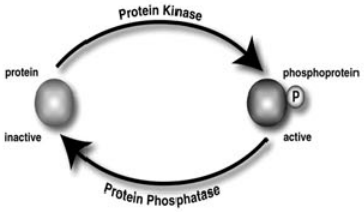
Chemical Neurotransmission In the Brain



- 'Slow' neurotransmitters, like dopamine, bind to receptor proteins at the surface of post-synaptic neurons.
- Activation of these receptor proteins leads to changes in second messenger molecules and a cascade of chemical effects involving protein kinases, and other cellular factors.
- These cellular cascades, in turn, control the activity of many essential neuronal proteins including ion pumps, ion channels, and neurotransmitter receptors by changing their state of phosphorylation

Intra-Cellular Therapies

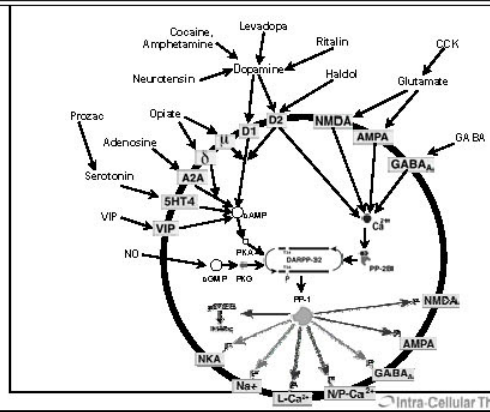
Protein kinases and protein phosphatases regulate protein phosphorylation



- The state of phosphorylation of proteins is determined by the activity of both protein kinases and protein phosphatases
- *In vitro* and *in vivo* methods have been designed to minimize artifactual post-mortem and post-treatment activity of kinases and phosphatases
- Phosphorylation state can be preserved following pharmacological or physiological treatments to provide a 'snapshot' of the state of phosphorylation at multiple sites

Intra-Cellular Therapies

Intra-Cellular Therapies *The Inside Track for CNS Drug Discovery*



Intra-Cellular Therapies

In Vitro and *In Vivo* Methods for Measuring Brain Phosphoproteins

In Vitro Slice Techniques

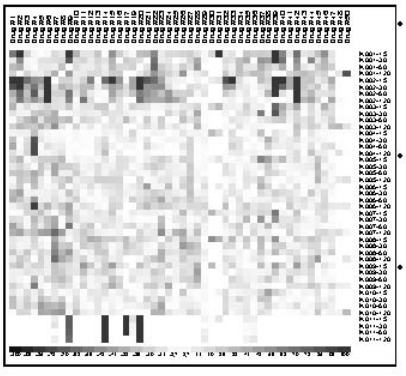
- Technique can be adapted to analyze drug actions in many brain regions (e.g., striatum, PFC, hippocampus, accumbens)
- Slice technique can be adapted to facilitate higher throughput drug screening (e.g., ED50 estimates)
- Slices offer an intact, anatomically-defined cell system in which to test region-specific drug effects
- Slice techniques enable testing in brain tissue of compounds which do not readily cross the blood-brain barrier

In Vivo Microwave Techniques

- Inactivation of brain enzymes by microwave irradiation enables estimates of *in vivo* levels of protein phosphorylation from mice treated systemically with pharmacological or physiological agents
- Microwave irradiation essential for preservation of labile phosphoproteins

Intra-Cellular Therapies

Measuring Protein Phosphorylation



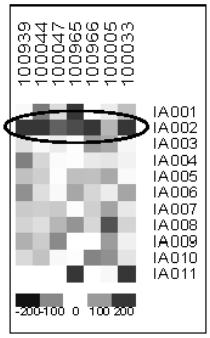
- The state of phosphorylation is detected using phosphospecific antibodies
- A panel of antibodies is used to evaluate 11 separate phosphosites.
- Spatial and temporal patterns of phosphorylation create a unique signature of drug action.

Intra-Cellular Therapies

PhosphoProfile of Antipsychotic Drug Actions

SITE IA1002		
Antipsychotic Drug	Mean ± SEM	
100939	*182+14	p=.0005
100044	*270+16	p<.0001
100047	*171+11	p<.0001
100965	*167 + 19	P<.01
100966	*241+10	p<.0001
100005	*137+4	p=.0096
100033	*153+18	p=.03

*significant at p<0.05



Intra-Cellular Therapies

CNS Profile can be implemented to:

- Generate a molecular signature of a class of compounds to serve as a reference for screening compounds of unknown mechanism of action
- Identify novel targets for future drug discovery efforts

Intra-Cellular Therapies

Gulf War Illness

- Gulf War Illness (GWI) is characterized by symptoms which include irritability, anxiety, headache, depression, poor concentration, memory impairments
- GWI may be associated with exposure to nerve agents (i.e., sarin), insecticides (i.e., DEET), and other compounds such as pyridostigmine bromide (PB) or a combination of these agents
- Nerve agents and PB inhibit an enzyme (acetylcholinesterase or AChE) that is critical for maintaining normal levels of the neurotransmitter acetylcholine in the brain
- As a result they cause supra-physiological levels of acetylcholine to occur in the brain and periphery

Intra-Cellular Therapies

GWI (Continued)

- Massive increase in acetylcholine levels in the brain leads to the activation of multiple nicotinic (12) and muscarinic (5) receptors
- Increasing brain acetylcholine has a highly complex secondary response
  - Activation of nicotinic and muscarinic receptors leads to secondary release of multiple neurotransmitters, including Dopamine, Glutamate, and GABA
- Signaling pathways that mediate effects of acetylcholine under these conditions are poorly understood
- An understanding of these pathways would provide targets that would greatly advance the search for therapeutic interventions for GWI

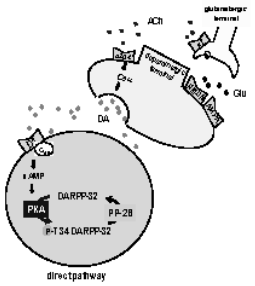
Intra-Cellular Therapies

ITI's efforts to identify targets for treatment of GWI

- Characterization of signaling pathways for acetylcholine
  - Pathways activated by physiological levels of acetylcholine resulting in nicotinic and muscarinic receptor activation
    - Supported by DAMD 17-03-2-0019
- Preliminary collaboration with USAMRICD to characterize pathways activated by nerve agents resulting in nicotinic and muscarinic receptor activation

Intra-Cellular Therapies

Elucidation of Nicotinic receptor signaling pathways

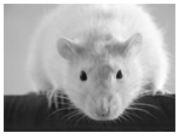


A scheme for the response pathway downstream of high levels of nicotine:

- Nicotine binding to α7 nicotinic receptors stimulates release of glutamate from glutamatergic terminals,
- Glutamate binding to NMDA and AMPA receptors on dopaminergic terminals drives bursts of dopamine release,
- This high-level dopamine signal stimulates D1 dopamine receptors on direct pathway neurons, leading to elevated phosphorylation of T34.

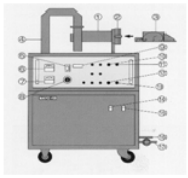
Intra-Cellular Therapies

Elucidation of Signaling Pathways Activated by Sarin Exposure

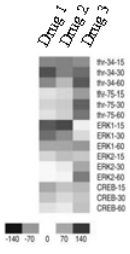


In Vivo Phosphoprotein Measurements
•Systemic administration of Sarin to rats in collaboration with Drs. T.M. Shih and John McDonough, USAMRICD

Focused microwave irradiation
Used to preserve phosphoproteins



PhosphoProfile of Sarin
•Monitor effect of Sarin at multiple phosphorylation sites
•Time-dependent responses (15-30 min)
•Dose responses (LD50, 0.5 LD50)
•Several brain regions including striatum



Intra-Cellular Therapies

A convulsant dose of Sarin (LD50) dephosphorylated several phosphoproteins

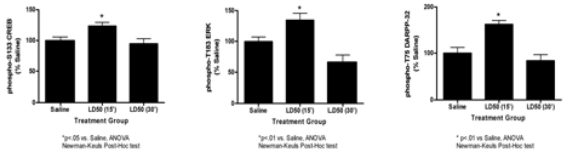
These include:

- *Spinophilin, a protein phosphatase 1 (PP1) targeting protein*
- *DARPP-32, at T34, the site controlling PP1 inhibition*
- *Glutamate receptors (NMDA-type)*

Intra-Cellular Therapies

Sarin (LD50) increases phosphorylation of several phosphoproteins

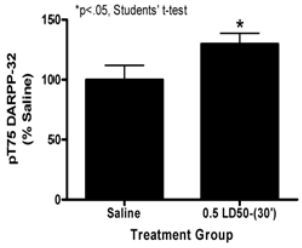
- *These include:*
  - *CREB, a gene transcription factor*
  - *MAP kinase, a growth factor-associated protein kinase*
  - *DARPP-32 at T75, a substrate for CDK5, a kinase involved in neuronal migration/development*



Intra-Cellular Therapies

DARPP-32 T75, a marker for Sarin exposure

- ***A sub-convulsant dose of Sarin increases <u>only</u> phosphorylation of DARPP-32 at T75, the CDK5 site***
  - *T75 may be a marker for Sarin exposure*



Intra-Cellular Therapies

Ongoing and Future Studies

- **Continue to delineate nicotinic and muscarinic receptor pathways**
  - Continue to identify additional targets for acetylcholine receptor activation
  - Create gene 'knockouts' for each muscarinic receptor
- **Use molecular biological techniques to discover molecules that interact with nicotinic and muscarinic receptors and modify their activity**
  - 'Two-hybrid' screens

Intra-Cellular Therapies

Strategy for Therapeutic Intervention in GWI

- **Generate complete map of cellular effects of sarin and other nerve agents**
  - Low-dose and high-dose exposure
  - Acute and chronic exposure
- **Identify targets common to these exposure conditions**
- **Screen chemical libraries to discover small molecules capable of modulating/reversing toxic effects of these agents**
  - Acute effects: anti-convulsant
  - Chronic effects: neural protectant/prophylactic
  - Test in animal models for GWI

Intra-Cellular Therapies


www.intracellulartherapies.com
Intra-Cellular Therapies