

**Research Advisory Committee on Gulf War Veterans' Illnesses**

September 15-16, 2008, Committee Meeting Minutes

Department of Veterans Affairs  
Washington, DC

**DEPARTMENT of VETERANS AFFAIRS**



**Research Advisory Committee on Gulf War Veterans' Illnesses**  
**Boston University School of Public Health**  
**715 Albany Street, T4W, Boston, MA 02118**  
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I hereby certify the following minutes as being an accurate record of what transpired at the September 15-16, 2008 meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses.

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/signed/

James H. Binns

Chairman

Research Advisory Committee on Gulf War Veterans' Illnesses

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## **Attendance Record**

### **Members of the Committee**

James H. Binns, Chairman  
Carrolee Barlow  
Floyd E. Bloom  
Daniel J. Clauw  
Beatrice A. Golomb  
Joel C. Graves  
Anthony Hardie  
Marguerite L. Knox  
William J. Meggs  
Mary Nettleman  
James P. O'Callaghan  
Steve Smithson  
Adam Such  
Roberta F. White

### **Consultant to the Committee**

Jack Melling

### **Committee Staff**

Sadie Richards  
Kimberly Sullivan

### **Designated Federal Officer**

William Goldberg

### **Guest Speakers**

Edward Kasarskis  
Ronnie Horner  
Eugene Oddone  
Marie Lynn Miranda  
Paul Levine  
Mitchell Wallin  
Melissa Kaime  
Han Kang  
Shannon Barth  
Jessica Maillard  
Gudrun Lange  
Karen Quigley  
Helena Chandler

### **Representative from the University of Texas Southwestern**

Robert Haley

## Abbreviations

ALS – Amyotrophic Lateral Sclerosis  
BBB - Blood Brain Barrier  
BUSPH - Boston University School of Public Health  
CAM - Chemical Agent Monitor  
CBT – Cognitive Behavioral Therapy  
CDC – Center for Disease Control  
CDMRP – Congressionally Directed Medical Research Programs  
CFS - Chronic Fatigue Syndrome  
CRADA – Cooperative Research and Development Agreement  
DFO – Designated Federal Officer  
DOD - Department of Defense  
DTI - Diffusion Tensor Imaging  
DU – Depleted Uranium  
DUA - Data Use Agreement  
EDTA – agent that can be used to evaluate kidney failure; 2-[2-(Bis(carboxymethyl)amino)ethyl-(carboxymethyl)amino]acetic acid  
FM - Fibromyalgia  
fMRI - Functional MRI  
GAO – U.S. Government Accountability Office  
GENEVA - Genes and Environmental Exposures in Veterans with ALS study  
FM – Fibromyalgia  
GI – Gastro Intestinal  
GIS - Geographic Information System  
GW - Gulf War  
GWI – Gulf War Illness  
GWIRP – Gulf War Illness Research Program  
HHS – U.S. Department of Health and Human Services  
ICD-9 – The World Health Organization’s International Classification of Diseases and Related Health Problems (9<sup>th</sup> edition)  
ISG - Iraqi Study Group, a.k.a. the Iraqi Survey Group  
LSU – Louisiana State University  
LTC – U.S. Army Lieutenant Colonel  
MOPP – Mission Oriented Protective Posture  
MRS – Magnetic Imaging Spectroscopy  
MS - Multiple Sclerosis  
NAPS - Nerve Agent Pre-treatment Sets  
NBC - Nuclear, Biological, and Chemical Officer  
NCI - National Cancer Institute  
NGWRC - National Gulf War Resource Center  
NIOSH - National Institute for Occupational Safety and Health  
OEF - Operation Enduring Freedom  
OIF - Operation Iraqi Freedom  
OIG - Office of the Inspector General (  
ORD – Veterans Affairs Office of Research and Development

RAC – Research Advisory Committee on Gulf War Veterans’ Illnesses  
SCI - Spinal Cord Injury  
UIC - Unit Identification Code  
UNMOVIC - United Nations Monitoring, Verification, and Inspection Commission  
UNSCOM – United Nations Special Commission  
US – United States  
USACHPPM - US Army Center for Health Promotion and Preventive Medicine  
USN – United States Navy  
UTSW - University of Texas Southwestern  
VA - Veterans Affairs (  
VISN - Veterans Integrated Service Network  
VX – nerve agent ((O-ethyl-S[2(diisopropylamino)ethyl]methylphosphonothiolate)  
WHO – World Health Organization  
WRIISC-DC – War-Related Illness and Injury Study Center at the Washington DC VA  
Medical Center  
WRIISC-NJ – War- Related Illness and Injury Study Center at the New Jersey VA  
Medical Center

**Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses  
September 15-16, 2008  
Department of Veterans Affairs, 810 Vermont Avenue, NW, Room 230,  
Washington, D.C.**

***Agenda***  
**Monday, September 15, 2008**

- |                      |   |  |
|----------------------|---|--|
| <b>8:00 – 8:30</b>   | <b>Informal gathering, coffee</b>   |  |
| <b>8:30 – 8:35</b>   | <b>Welcome, introductory remarks</b>  | <b>Mr. Jim Binns, Chairman<br/>Res Adv Cmte Gulf War Illnesses</b>                           |
| <b>8:35 – 9:30</b>   | <b>Clinical Profiles of ALS in GW veterans</b>                                      | <b>Dr. Edward Kasarskis<br/>VA Medical Center, Lexington, KY</b>                             |
| <b>9:30 – 10:15</b>  | <b>Update on the investigation into the ALS<br/>Outbreak among 1991 GW veterans</b> | <b>Dr. Ronnie Horner*<br/>University of Cincinnati</b>                                       |
| <b>10:15 – 10:30</b> | <b>Break</b>  |  |
| <b>10:30 – 11:15</b> | <b>National Registry of veterans with ALS<br/>And GENEVA study</b>                  | <b>Dr. Eugene Oddone<br/>Durham, NC VAMC</b>   |
| <b>11:15 -12:00</b>  | <b>Spatial Analysis of ALS in GW veterans</b>                                       | <b>Dr. Marie Lynn Miranda<br/>Duke University Medical Center</b>                             |
| <b>12:00-12:30</b>   | <b>A Neurological Evaluation of GW veterans</b>                                     | <b>Dr. Paul Levine<br/>George Washington University</b>                                      |
| <b>12:30 - 1:30</b>  | <b>Lunch</b>  |  |
| <b>1:30 - 2:00</b>   | <b>Update of VA Gulf War research</b>   | <b>Dr. William Goldberg<br/>VA Office of Research and Development</b>                        |
| <b>2:00 – 2:15</b>   | <b>Break</b>  |  |
| <b>2:15 – 3:00</b>   | <b>Update of UTSW Gulf War research</b>   | <b>Dr. Robert Haley<br/>University of Texas Southwestern<br/>VA Dallas Healthcare System</b> |
| <b>3:00 - 3:30</b>   | <b>VA Multiple Sclerosis Study</b>  | <b>Dr. Mitchell Wallin<br/>MS Center of Excellence, East<br/>VA Washington, DC</b>           |
| <b>3:30 – 4:15</b>   | <b>Environmental exposures during the<br/>Gulf War</b>                              | <b>Mr. Joel Graves<br/>Res Adv Cmte Gulf War Illnesses</b>                                   |
| <b>4:15 - 4:45</b>   | <b>Public comment</b>   |  |

**\*participating by phone**



**Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses  
September 15-16, 2008  
Department of Veterans Affairs, 810 Vermont Avenue, NW, Room 230,  
Washington, D.C.**

***Agenda*  
Tuesday, September 16, 2008**

- |                      |   |   |
|----------------------|---|---|
| <b>8:00 – 8:30</b>   | <b>Informal gathering, coffee</b>                 |   |
| <b>8:30 –9:15</b>    | <b>CDMRP Gulf War program update</b>              | <b>CAPT. Melissa Kaime<br/>Congressionally Directed Medical<br/>Research Program</b>                |
| <b>9:15 – 10:15</b>  | <b>Washington WRIISC research update</b>          | <b>Dr. Han Kang<br/>VA Washington, DC</b>   |
| <b>10:15 – 10:45</b> | <b>New Jersey WRIISC research update</b>          | <b>Dr. Karen Quigley<br/>Dr. Helena Chandler<br/>Dr. Gudrun Lange<br/>DVA NJ Health Care System</b> |
| <b>10:45 – 11:00</b> | <b>Break</b>                                      |   |
| <b>11:00 – 11:30</b> | <b>Secretary addresses the Committee</b>          | <b>Secretary James Peake<br/>Department of Veterans Affairs</b>                                     |
| <b>11:30 – 12:00</b> | <b>Update of recent GW research</b>               | <b>Dr. Beatrice Golomb<br/>Res Adv Cmte Gulf War Illnesses</b>                                      |
| <b>12:00 – 12:15</b> | <b>Federal Advisory Committee ethics training</b> | <b>Mr. Jonathan Gurland</b>   |
| <b>12:15 – 12:30</b> | <b>RAC Committee report update</b>                | <b>Mr. James Binns, Chairman<br/>Res Adv Cmte Gulf War Illnesses</b>                                |
| <b>12:30 – 1:00</b>  | <b>Public comment</b>                             |   |
| <b>1:00</b>          | <b>Adjourn</b>                                    |   |

## **Day 1**

The September 15-16, 2008 meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses was held in Room 230 at the Department of Veterans' Affairs, 810 Vermont Avenue, NW, Washington, D.C.

### **Welcome, introductions & opening remarks**

James H. Binns, Chairman

Chairman James Binns called the meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses (hereinafter referred to as the "Committee") to order at 8:30 am. Chairman Binns welcomed everyone to the meeting, including the invited speakers, members of the committee, and members of the public.

Chairman Binns began by welcoming Dr. Dedra Buchwald to her first Committee meeting. Dr. Buchwald is from the University of Washington, and is an expert on CFS. Chairman Binns then extended a special welcome to several individuals in the audience, including the group of veterans from the National Gulf War Resource Center (NGWRC) and the contingent of four audience members from the United Kingdom, including individuals from the Royal British Legion and Lord Morris and Lady Morris from the House of Lords.

Chairman Binns then noted that this is the first Committee meeting to welcome call-in attendees by telephone. He explained that this meeting would facilitate participation from an auditing point of view, but that the Committee hoped to allow call-in participation during the public comments section in the future.

Chairman Binns reminded everyone that the release of the Committee's major report would be delayed until November 17, 2008. Chairman Binns then noted that Secretary Peak had graciously agreed to still participate in the Committee meeting the following day at 11:00 am, in order to meet everyone and to present certificates to new members of the Committee. Chairman Binns mentioned that the agenda would be subject to a few changes in light of several attendees' unexpected travel and illness-related attendance issues. Chairman Binns concluded by turning the microphone over to Dr. White to introduce the first speaker and the Committee staff members.

### **Introduction of Dr. Kasarskis and Committee Staff**

Dr. Roberta White, Scientific Director  
Chair, Department of Environmental Health, BUSPH

Dr. White began by introducing and thanking committee staff members Kim Sullivan and Sadie Richards for organizing the committee meeting and assisting the Committee at BUSPH. Sadie joined the Committee as the new Research Assistant on September 9, 2008.

Dr. White then introduced Dr. Edward Kasarskis.

**Clinical profiles of Amyotrophic Lateral Sclerosis (ALS) in Gulf War veterans**

Dr. Edward Kasarskis  
Chief, Neurology Service, VA Medical Center, Lexington, Kentucky  
Cynthia Shaw Crispen Chair of for ALS Research, Dept. of Neurology,  
University of Kentucky, Lexington

Dr. Kasarskis provided an overview of Amyotrophic Lateral Sclerosis (ALS) to include the clinical definition and symptomatic presentation of the disease. In his presentation (See Appendix A – Presentation 1), Dr. Kasarskis addressed the following questions in detail: What is ALS? What are the challenges to accurately diagnosing the disease? What are the broad theories as to what causes ALS? How is ALS managed from a clinical standpoint? After this general presentation Dr. Kasarskis gave an update of new survival data from his current Gulf War study, which “examines whether there is anything peculiar about the phenotype of Gulf War veterans who developed ALS” (e.g. does there appear to be a Persian Gulf variant of ALS?). Dr. Kasarskis found that ALS in Gulf War veterans was comparable to ALS afflicting the general population (including non-deployed veterans). However, Dr. Kasarskis’ study did find statistically significant shorter survival (17 months) in deployed versus non-deployed veterans of the Gulf War era. See Appendix – Presentation 1 for more detailed findings, including potential factors associated with this difference in survival time.

Dr. White introduced Dr. Ronnie Horner, and requested that questions for Dr. Kasarskis be held until after Dr. Horner’s presentation.

**Update on the investigation into the ALS outbreak among 1991 Gulf War veterans**

Dr. Ronnie Horner  
Chair, Department of Public Health Sciences, University of Cincinnati College of  
Medicine

Due to inclement weather, Dr. Horner presented via phone, accompanied by PowerPoint slides (See Appendix A – Presentation 2). Dr. Horner first provided a brief history of the study on the ALS outbreak among 1991 Gulf War veterans. In his presentation, Dr. Horner examined epidemiological data to address the following questions: Is the outbreak real? Is the outbreak over? What is the etiology of the outbreak? Is this outbreak a signal of a broader risk that might be associated with military service?

Dr. White thanked Dr. Horner for his presentation, and opened the floor to questions from the Committee members for both Dr. Horner and Dr. Kasarskis.

Dr. Meggs, a member of the Committee, asked Dr. Kasarskis if he had seen similar cases to that of one patient that had been referred from Neurology to his Medical Toxicology

clinic. This patient was an electrical worker with a remarkable exposure to transformer fluids, including PCBs, who developed lower motor neuron disease, and was given a clinical diagnosis of ALS. Dr. Meggs described how this patient's condition "progressed, and then when he became disabled and was taken off the job the progression of his disease ended and he stabilized. He didn't get any better but he didn't progress." Dr. Meggs then asked if Dr. Kasarskis sees that type of scenario often.

Dr. Kasarskis responded that every once in a while a patient will stabilize, for reasons that are really unknown. He explained that surviving motor neurons are known to have sprouts that can re-innervate muscle fibers, so that previously inactive muscle fibers can become reactivated. It is believed that waves of de-innervation and re-innervation occur during the course of ALS. In many neurodegenerative diseases, there is a critical mass of neuronal loss (~50% in ALS) that has to occur before somebody even realizes that they have a condition. Dr. Kasarskis acknowledged that removing patients from potential disease etiology/ies might reduce their symptoms.

Dr. Clauw, a member of the Committee, then asked whether Dr. Kasarskis or Dr. Horner were dismissive of the notion that this could be a broader problem with all wars, not just the Gulf War. Dr. Clauw expressed his belief that the Weisskopf study (which found that individuals who served in the military were at elevated risk for ALS compared with those who had never served in the military) was a very well-done study which should invoke questions about whether ALS is a problem that has been associated with all wars. Dr. Clauw was concerned that if ALS was not a problem specific to the Gulf War that a lot of the things that had been funded didn't then make a lot of sense. Dr. Clauw then argued that (in his opinion) no existing data counters the Weisskopf findings, because of the way they had been conducted (with control groups that weren't in the military, which he argued wouldn't have picked up a non-specific effect of war).

Dr. Kasarskis deferred to Dr. Horner's comments first.

Dr. Horner said that, though the Weisskopf study was well done, and the Institute of Medicine regards it as the highest level of evidence, the problem he has with it is the lack of an identified mechanism for that would associate certain different wars with the onset of ALS. He doesn't think other cohorts have been studied to determine whether or not it is truly ALS that is being seen. He also expressed doubt that the Weisskopf group had tracked whether or where their study participants had actually been deployed during periods of conflict.

Dr. Kasarskis then responded, saying that he agreed with Dr. Clauw's comment that the Weisskopf study points to an effect of military service. He also said that he disagreed a little bit with Dr. Horner, and stated that he doesn't believe researchers should be seriously bound on having an explanation at hand, explaining that he thinks the research is still trying to define a phenomenon, and whether it exists or not. Dr. Kasarskis then noted that Gulf War veterans constitute a very unique, fairly controlled population, unlike other wars (e.g. the Gulf War – and period of potential exposure – was short and less open-ended than other wars like Vietnam). This makes the experimental design – and

resulting findings – more sound (comparable, in Dr. Kasarskis' mind, to an animal model study). Dr. Kasarskis also expressed appreciation for Dr. Horner's nice portrayal of the data set with his epidemic curve. Dr. Kasarskis stated his opinion that the Gulf War service (in terms of the significantly large number of veterans who served, and the short duration of service) is "allowing a signal to come out."

Dr. Clauw then asked everyone to look at the data, claiming that "the odds ratio in the Weisskopf study is almost identical (two-fold)" to what Kasarskis found in his study.

Dr. Kasarskis agreed.

Chairman Binns then clarified that "the comparison being made in Dr. Kasarskis' and Dr. Horner's studies is between military people who were not deployed and military people who went to the Gulf." He therefore pointed out that if the Weisskopf study is correct, there is still double the rate of ALS over the base rate in military people in this study. So, it is not that everyone in the military has a two-fold risk; if everyone does, fine, but people who were in the Gulf have a four-fold risk, if you want to look at it that way."

Dr. Kasarskis then pointed out that the Weisskopf study had a more representative distribution of population than this Gulf War study. "Again, I am trying to emphasize how young this is in the world of ALS, whereas I believe the median age group from the Weisskopf study was what you would expect from a normal population. So you get into the thing that Dr. Horner alluded to in terms of the comparison group in the Gulf War study were equally physically fit, and had similar types of experiences going into it, and differed by virtue of where they were doing their military service in general. You'll have to get some military expert to verify that, but from what I've read and understand, that is the case."

Dr. Horner then clarified that he was not saying that the Weisskopf study is wrong. "Military service could convey a risk, but it's going to manifest itself in the longer term. What we're seeing here in the Gulf War is something among relatively young men and women that was very explosive, very dramatic, very clear. Something happened to them while they were deployed, and we see this elevated risk. If the military has additional risk, we may see it arrive in this group over time, as we go out further, but it's going to be when they are much older. Here we have a very young population who manifested a very rare disease in a very unusual way."

Dr. White then mentioned the group at the Boston University School of Public Health (BUSPH) that has a monthly discussion meeting on Gulf War-related illness problems, and how the group spent the last meeting discussing the ALS issue. Marc Weisskopf, a neurotoxicologist at the Harvard School of Public Health, is a member of this group. Dr. White elaborated on how the group's discussion focused on two things: whether there was some additional risk associated with the Gulf War that increased the probability of ALS and, secondly, the issue of what being in the military/military experience does to people's health – which is a question that can't be answered with the existing data. Dr. White noted that Dr. Weisskopf is very interested in the question of military families and

gene-environment interactions and, without the draft – with the voluntary army – how some of these neurodegenerative diseases that have genetic components are really going to play out in the future. But Dr. White stated that she thinks one of the really important things about GW illness and the GW experience is that it has really led researchers to look at what happens to all people when they're deployed, and then how special circumstances associated with particular theatres and/or war experiences specifically affect the illness of individuals.

Dr. White then asked two questions. Regarding etiology, she asked if either Dr. Kasarskis or Dr. Horner had any gut-level feeling about what the most important factors might have been in determining the GW-related illnesses. She then asked if “the ALS story” reveals any clues relevant to people with unexplained illnesses.

Dr. Horner responded by saying that he believes that something specific happened to these individuals during that period of deployment, and that Dr. Miranda's yet-to-be-presented GIS analysis (Presentation 4) would “tease into that,” adding that she is looking at specific places in *space*. Dr. Horner asserted that researchers also need to look at the identified spaces with regard to *time* in order to explore more fully for potential exposures. He added that, until recently, researchers had just two exposures to look at – the low-level nerve agent plume from the Khamisiyah explosion, and the oil well fire smoke. Dr. Horner then recounted a recent telephone conversation he and Dr. Miranda had with an individual in the military who presented some very interesting data about the presence of heavy metals in the desert soil. Once you break up the desert varnish you are exposed to the metal concentrations in the soil, and there is some work that suggests that exposure to heavy metals is associated with ALS, so this is another avenue that he feels could be explored. He thinks it makes sense to at least consider it and look at it. Prior to having that conversation he had no idea why anyone would be seeing what was being found physically (e.g. “mini hot spots that popped up”). Dr. Horner then commented that the dust is very fine and blows all over in the region. He believes that ALS might just be one extreme of a continuum of neurotoxic effects that could arise due to gene-environment interaction. However, he adds that if he had been asked this a year ago he would have had another opinion, because it's an evolving situation. He thinks researchers need to continue to do these studies and that the data may well allow researchers to find the etiology of the outbreak, and may have broader implications.

Dr. Kasarskis responded by calling for more epidemiological studies, in terms of what specific defined populations may or may not have been exposed to as a group, because these cases – although few in number – emerged from a group of people with a common exposure of some sort, if it proves to ultimately be an exposure. However, Dr. Kasarskis cautioned that every single patient has some personal theory of what caused their illness, and that arguing from an n of 1 makes good press and an interesting story, but it doesn't get us anywhere scientifically. Therefore, he asserted, population-based research is essential.

Dr. Jack Melling, Consultant to the Committee, then asked the question of whether the “bipolar nature of the epidemiology would be consistent with all of the people having

essentially a single exposure, and then some of that group having a genetic makeup that made them respond to that earlier exposure versus the second group that took longer to respond?”

Dr. Horner responded that he wasn't sure that the nature of the epidemiology is bimodal, especially given the small numbers of those manifesting ALS on the early edge of the curve.

Chairman Binns recalled that there were two examples of anecdotal cases where people who developed ALS had associated it in their own minds with exposure to pesticides immediately after the war. He then asked if either Dr. Horner or Dr. Kasarskis were conducting or aware of any studies looking at post-war exposures that might also, along with the genetic thoughts that Dr. Melling expressed, be the second event that could explain some of this.

Dr. Horner had not looked at post-deployment exposure.

Dr. Kasarskis added that the data are hard to come by, and that many of these individuals have died, so that even anecdotal reminiscences will be lost.

Dr. Mary Nettleman, a member of the Committee, asked whether the results may be reflecting an acceleration of already inevitable ALS cases. In other words, she asked, “was there something about these people that made them susceptible” to something that happened in combat? She added that, if that were so, those cases should have been depleted from the population resulting in a dip in incidence rate far below the population of non-deployed veterans in the future. She added therefore added that continuing the research with this in mind could provide some epidemiologic data that could help figure out what is going on. Dr. Nettleman then noted that the “little hump” in 1991 could have been lead cases that actually were incident before the war, and this could simply be a lead bias.

Dr. Kasarskis agreed that systematically following the cohort over the next 15-20 years, looking for new incident cases in the future, could begin to answer the first question Dr. Nettleman raised. Dr. Kasarskis then added that one of the theories that people have put forward is that affected individuals might have a susceptible group of motor neurons which could be “knocked down to a certain level” by a particular agent, but that the individual would then proceed aging (and experiencing neuronal “dropoff”) at whatever rate they're aging until they would hit the neuronal threshold for disease expression at some point in the future.

Dr. Nettleman reiterated that this theory/possibility argues for continuing the research.

Dr. Kasarskis agreed, commenting that the question Dr. Nettleman raised expands strongly to other neurodegenerative diseases, and he suggested that, in a sense, ALS is a prototype because there are things to measure in a quantitative sense in terms of disease progression. The other thing that he pointed out was that, in people under 40, there are

more cases of ALS in the GW population than the rest of the world's established/well done epidemiological literature. This makes comparisons difficult, and is going to temper what researchers are permitted to conclude about this population.

Chairman Binns then asked Dr. Horner if he could comment on the *ALS-like* cases he had mentioned when speaking to the Committee several years ago.

Dr. Horner did not recall saying this, but admitted he may have said it.

Chairman Binns then proceeded to ask whether there is ongoing work to look post-2001, since if this is a limited outbreak and it's now over, that's a comforting factor for current veterans.

Dr. Horner stated that they should probably track the cases out. The VA ALS registry would be able to provide those data if it continues on. Personally, he believes, based on the evidence that he's presented, that the risk has dropped – that the risk period has passed. He would not expect in this cohort to see another rise in the occurrence of ALS, which is why I'm very focused on looking at an etiology that occurred while they were deployed in the Persian Gulf area. They will develop ALS at an expected rate for somebody their age, unless of course military service conveys some kind of longer-term risk – then that would be manifested.

Before closing, Chairman Binns invited Dr. Haley to comment, since he also published research on this, in order to find out what his ongoing studies now might be looking at.

Dr. Haley, of the University of Texas, Southwestern (UTSW) then asked Dr. Horner if he did Sartwell modeling, if he looked at the epidemic curve data for each of the two clusters separately. He noted that the first cluster was stacked up against the beginning of the war period, but asked if Dr. Horner had looked at the second cluster by itself (essentially "playing a statistical game"), since it would probably be a very strong rejection of the null hypothesis if the clusters were found to be separate. Dr. Haley stated that he thought the Committee ought to put in a strong recommendation that this work be supported strongly and go on indefinitely "because it looks like the epidemic is over." He believes that has two important implications: One is that it appears to have been an epidemic, and he said that he thought this is the first time that's been said. Secondly, although hopefully it's over and the period of risk is gone, he pointed out that the risk had not gone below one, back to the baseline level, suggesting that it might be "smoldering on" with a few people whose susceptibility has been prolonged. Dr. Haley expressed concern that there could be a third peak, and no one would know that until the third peak occurred, and so he believes continued surveillance of this is really essential. Dr. Haley also suggested that the Committee refer this evidence and recommend to the other VA advisory committee that they consider this evidence, because he believes the service connection status of ALS veterans is still an ongoing, temporary, renewable issue that could be reconsidered in the future and he thinks this evidence makes a very strong case that ALS service connection should be permanent for GW veterans.



Steve Smithson, member of the Committee, commented that supposedly the Secretary of the VA has drafted some regulations (that are still going through the process) that would make ALS indefinite presumption for anybody who served in the military. But he stressed that he has not seen anything certain in writing.

Chairman Binns then thanked Dr. Haley, Dr. Kasarskis and Dr. Horner for their presentations, and briefly stopped the meeting for a 10 minute break.

At 11:00am, the meeting reconvened.

Dr. White introduced Dr. Eugene Oddone.

**National Registry of veterans with ALS and GENEVA study**

Dr. Eugene Oddone  
Director of the Center for Health Services Research in Primary Care at the  
Durham VAMC  
Professor of Medicine and Vice Dean for Research at Duke University School of  
Medicine

Dr. Oddone spoke about the objectives, methodology and progress of compiling the National Registry of Veterans with ALS, including the DNA Bank component (See Appendix A – Presentation 3). Dr. Oddone pointed out that the key thing about the Registry is not just to have it, but to get scientists access to it and to begin to do studies on etiology, and/or to try to allow these veterans into treatment trials (though, unfortunately, there are not too many treatments currently available). Dr. Oddone then spoke about one of the studies utilizing the Registry data: the Genes and Environmental Exposures in Veterans with ALS (GENEVA) study. This study, led by Dr. Silke Schmidt, is the largest study that has been approved to use the Registry's DNA data. Participants (cases and controls) are still being recruited for this study. Dr. Oddone concluded by giving an overview of additional studies currently utilizing the Registry data.

The floor was then opened up to questions.

Dr. Buchwald, whose background deals with chronic fatigue syndrome and FM, (where accurate diagnosis is very difficult) asked for confirmation that the cohorts of patients in both Dr. Oddone's and Dr. Kasarskis' studies had never actually been examined by a single person or group of people.

Dr. Oddone confirmed that this was true.

Dr. Buchwald then asked Dr. Kasarskis about his list of neurologic disorders that mimic ALS – most of which she had never seen or heard of. Dr. Buchwald asked how the neurologists in the Registry came to a consensus regarding each patient's diagnosis, noting that, "particularly in the first study, a small amount of misclassification will actually wipe out his results." She asked the question based on her own experience

looking at lots of medical records for studies and noticing that sometimes these subtle differences in symptoms and diagnostic criteria are just not noticed or recorded, “so I just wondered if you could comment on that.”

Dr. Kasarskis replied that it was a very legitimate question. He said that in the first GW study his group actually had two out of the five neurologists independently review each record on the basis of the El Escorial criteria (which he alluded to in his presentation). His research team did not ask the people providing medical records to do any editing, so his research team had records from multiple sources – physical therapists, other neurologists – and went through them so that they didn’t have a selection that way. In the first study both neurologists had to agree on the diagnosis. If there were questions they were resolved either by Dr. Kasarskis doing a third review and breaking the tie or by conducting consensus conference calls. Dr. Kasarskis said that, “basically, everybody really was agreeing that they saw and interpreted the same pieces of information.” He also noted that his study only included a small number of cases that would have been difficult to diagnose, and that they had been screened by two neurologists in the field. Dr. Kasarskis admits that Dr. Buchwald is right, that his research teams didn’t happen to examine any one of these patients, unless they happened to get one of their own patients that was sent on (to the Registry). For Dr. Oddone’s Registry, the decision had been made that they would use one neurologist since there was basic agreement. The one thing that he particularly liked about the flow of information to the Registry was the telephone screener that Dr. Oddone briefly mentioned, stating that if people passed through that screener there was a 93 or 94 percent chance that upon subsequent medical review the diagnosis would be supported as ALS. He concluded that actually the two or three questions in Dr. Oddone’s telephone-based screener are very powerful to filter through the population. But he agreed that there would be some error one way or the other. He mentioned that those who never came to medical attention would of course not be counted, so there could be mis-ascertainment regardless of deployment status, but the reason the El Escorial criteria were drawn up was precisely to facilitate research so people would fall back on the same set of criteria. He therefore concluded that it was reasonably certain that his study is dealing with bona fide ALS.

Dr. Oddone then expanded on the screening criteria, stating that the criteria classification is “definite” “probable” or “possible” ALS. He noted that one of the slides that Dr. Horner showed (in the first Persian Gulf War study) was a sensitivity analysis where he limited it to the “definite” cases. He added that Dr. Silke Schmidt is doing the same thing with the ALS genetic epidemiology study, so she has that classification system of “definite” “probable” or “possible” as well, and that one of the things they’ll do is some sensitivity analysis on the whole sample, limiting it to just the “definites.” He added that he keeps track of the patients every six months, and so subsequent medical records are requested for those who are not “definite.” They then go back to look at the records and if a patient’s El Escorial criteria goes up they are reclassified. But, he added, it is a clinical-based decision. He noted that, from the very first study (as Dr. Kasarskis said) the agreement was near-perfect (he did not have the exact figure) between neurologists, which is why they chose to use only one neurologist’s diagnosis for the Registry.”

Dr. White then thanked the presenters and introduced Dr. Marie Lynn Miranda.

**Spatial Analysis of ALS in GW veterans**

Dr. Marie Lynn Miranda

Director, Children's Environmental Health Initiative at Duke University

Dr. Miranda and her research group first constructed a Geographic Information System (GIS) to characterize troop movements in the Gulf War theatre, then examined whether the GIS revealed spatial pattern(s) in the locations of persons who eventually developed ALS (See Appendix A – Presentation 4). In her study, Dr. Miranda created a unified spatial representation (using GIS) of information on ALS cases (identified through the National Registry of Veterans with ALS), data on troop movement, and information on potential exposure to chemical warfare agents in and around Khamisiyah. By analyzing the data using Bayesian Poisson regression analysis, Dr. Miranda concluded that specific geographic locations of troop units are associated with an increased risk for subsequent development of ALS, and that there is also evidence of increased risk associated with potential exposure at Khamisiyah.

After the conclusion of Dr. Miranda's presentation, Dr. William Meggs commented on the controversy over the Khamisiyah plume (i.e. that the meteorological data is classified for that day), and he asked how Dr. Miranda handled this issue in her study of Khamisiyah exposure.

Dr. Miranda replied that her research team just took the data that was given to them from US Army Center for Health Promotion and Preventive Medicine (USACHPPM), which she believes was the U.S. Government Accountability Office (GAO) plume that was provided, and her team took it as [a binary variable of] 0/1 (or exposed/unexposed) to determine the Unit Identification Codes (UICs). Dr. Miranda then noted that, having heard the various things about the controversies over how those plumes were constructed and not getting wind direction correct, etc., she finds it pretty amazing that with a simple 0/1 binary variable her team is finding a posterior probability as high as 0.89. So her team accepted the data's validity. She added that if people wanted to give alternative constructions of the plume, it would be very straightforward for her team to put that in and redo the spatial analysis. She expressed interest in doing so, saying that she had such additional sensitivity analyses in mind should her current grant proposal get funded.

Dr. Meggs then asked about the "two big hot spots" that appeared in Dr. Miranda's spatial analysis. He noted that one looked like it was near Khamisiyah, and asked if Dr. Miranda had any clue about the other one.

Dr. Miranda said that the other hot spot was over water, and that there may be something occupational going on. However, she also cautioned that the static image (as opposed to the video/continuous display she had been unable to show at the meeting) would more adequately portray the discreet mapping and gradients.

Dr. Miranda then asked the Committee if they had any ideas about what latent variable(s) might account for the spatial representations her analysis revealed (i.e. what factors might be associated with the spikes in increased risk).

Dr. Jack Melling then asked about potentially confounding factors, and for confirmation that he understood the findings correctly. Dr. Melling noted that, almost regardless of where a unit was in the area, it is known that people were being exposed to potentially neurotoxic materials – such as NAPS tablets (in which the active ingredient is PB), organophosphates, and pesticides. He then asked if this general exposure to potential neurotoxins was that something Dr. Miranda had to account for in her analysis, or whether the way she did the spatial analysis automatically controlled for that, and if so, then he guessed that his interpretation was that “what emerges for analysis becomes even more powerful, because it’s come up above all that background stuff.”

Dr. Miranda confirmed that her study controlled for these variables (other chemical exposures) and that the findings therefore show risk that has emerged above the background exposures.

Dan Clauw then asked Dr. Miranda if her study used the same USACHPPM data used by Dr. Kang and others who have found no association between where people were and their broader set of symptoms.

Dr. Miranda said she would have to go back and look at the papers. She believes there were a couple of different plumes that were constructed, but that she wasn’t sure which plume data Dr. Kang and others used. She used the GAO plume data that USACHPPM provided.

Dan Clauw then posed a question regarding which branches of the military/which groups that had served in the GW were being found to be at higher risk of ALS and GW Illness more broadly. Based on the data presented at the day’s presentations, he felt that air force personnel (vs. people on the ground) appeared to be most at risk (driving the odds ratio), which didn’t make sense to him given the potentially toxic triggers that had been discussed.

Dr. Miranda then clarified that in Model 4, where areas of elevated risk were identified, branch of service has already been controlled for.

Dan Clauw said he understands this but still argued that her univariate risk was still very high for the air force personnel when Dr. Miranda presented the data.

After some deliberation, Dr. White called on Denise Nichols, a Major from the U.S. Air Force, to speak.

Maj. Denise Nichols noted that the two groups that appeared to be at elevated risk were the air force, followed by the army. The air force did the aerial bombings of the chemical facilities. She suggested looking at the altitude they were at – to see if exposure levels got

up to the air crew. She also mentioned that, when considering exposure among members of the air crew, oxygenation and physiology come into effect, and she postulated that it could be the oxidative stress factor combining to exert an effect. Maj. Nichols added that it was important for researchers to differentiate between 1) the pilots and the flight crews of the pilots that did the bombing, and 2) the air force ground crew. She urged the researchers to put the personnel data in with the system and separate out the different groups. Lastly, Maj. Nichols added that another thing to think about would be members of the army such as those flying helicopters and other types of lower altitude aircraft.

Dr. Clauw replied that this should be a very simple question to answer, given the relatively low number of people that have developed ALS – are people who were going up in the air or were people on the ground the ones who seem to be developing ALS?

Maj. Nichols agreed, noting that keeping track of individuals' specialty codes would help tease some of this out.

Dr. Miranda replied that this information is not in the Registry.

Dr. Oddone then said that occupation was part of the Persian Gulf War I study, which found that both the air force and the army were at elevated risk. He then added that since there were only 107 cases in that study, “drilling down” into individual occupations within that cohort would result in a loss of power to draw accurate conclusions. He added that he has included occupational information, but he didn't have the answer about whether they were all pilots.

Dr. Melling then asked if it would be true to say that the majority of air force people were ground crew rather than air crew.

Maj. Nichols replied that there were the forward air controllers, as Chairman Binns reminded her, that were “up there forward.” There were also medical evacuation hospitals that were all along the border. There were a large number of personnel that were medical evacuators. Maj. Nichols noted that the air crews were mostly based at different points in theatre, and over in Thunray. “The 130s were coming out of country, or bedded down at night.”

At this point Chairman Binns apologetically interrupted, noting that the Committee probably can't answer this question today, but thanked Maj. Nichols for the information. He then asked if there were any further questions for Dr. Miranda?”

Ms. Marguerite Knox, a GW veteran and member of the Committee, then noted that Mr. Tim Bullman and Dr. Han Kang had done some GIS mapping of the higher rates of brain cancer in GW veterans. She asked Dr. Miranda if she had looked to see if the regions that those researchers identified (that were exposed to Khamisiyah) overlap with her conclusions.

Dr. Miranda said she hadn't looked at this. The analysis she had just presented today was literally hot off the press – and hadn't actually come out yet. But she said she was very interested in looking at other health end points (e.g. FM, PTSD, etc.) now that methods to do spatial analysis appropriately exist. Dr. Miranda added that there is also the whole “gridding technique” (which took a long time to develop) to see whether these hot spots are the same or different for different disease end points.

Dr. Nettleman then asked a question then asked about the significance/possible events/exposures near the arrow on slides 16 and 19 of Dr. Miranda's presentation.

Dr. Miranda said she has asked that question (is there something special here that we should be thinking about?) on numerous occasions to people at Veterans Affairs, the Department of Defense, USACHPPM, but had received no answer.

Dr. Nettleman followed up, asking whether there was a major city at that location.

Someone from the audience mentioned the port, Al Jubayl.

Dr. Miranda noted that “now somebody is saying something,” and Dr. Nettleman concluded that the question was ongoing.

Anthony Hardie, a GW veteran and Committee member, thanked Dr. Miranda and commented that the arrow points to an area just east of the port Al Jubayl. He served in that area for about 4-5 weeks, and he commented that it looked like the area of elevated risk spreads westward, noting that there weren't blocks of U.S. troops the further west one went from that area. There were marine troops that were along the east coast, and then his troop got into areas that were controlled by coalition troops. He then asked if Dr. Miranda had any sense for how many people would have been in that area. Obviously they weren't evenly dispersed, and he commented that the orange area down by the northeast coast of Africa didn't correspond with the small number of U.S. ground troops that would have been stationed in that area, so he asked Dr. Miranda to talk a little about that.

Dr. Miranda replied that there were a total of 230 different UICs that passed through that hot spot, and the UICs were as large as 850 troops.

Anthony Hardie asked whether Dr. Miranda had a sense for geographic place names that were in that area, commenting that her map was “awfully small,” and that Kuwait appeared as a “tiny dot” making it difficult to see.

Dr. Miranda replied that she was hearing many people [veterans] in the audience off to her right saying that it's associated with Al Jubayl. She noted that in her discussions with people from USACHPPM that various possibilities were raised, but that she did not think the answer was Al Jubayl. She did say she would have to go back and overlay a lot of other geography in order to test the possibility, though.

Dr. Miranda continued, saying that she's tried to go through this with her DOD collaborators, to try to say what is it that's specific about these geographic areas, and they're still trying to figure some of that out. What she said she wants to emphasize is that although everybody likes to target in on the red hot spots, there are many areas – e.g. that whole orange-toned area – that have better than 50% (and quite a bit of it is in the 60-70%) posterior possibility, and that's a pretty large area. It's not that one concentrated red area. She said that she looks at this map and thinks about the preponderance of the orange.

Dr. White thanked Dr. Miranda for her presentation and introduced Dr. Levine, who has studied cancer and CFS for many years. This has led to research on GW veterans. He has also worked on cancer patterns in GW veterans, and the focus of his talk today is attempting to define GW Syndrome based on his CFS definitions.

### **Neurological Evaluation of GW veterans**

Dr. Paul Levine

George Washington University School of Public Health and Health Services

Dr. Levine, a multidisciplinary epidemiologist, presented an overview of a joint effort between the VA and George Washington University School of Public Health, which was focused on clarifying the definition for GW Syndrome (See Appendix A – Presentation 5). Basically this study had 3 phases – a factor analysis of a large survey conducted by Dr. Kang et al. and the VA, a clinical and epidemiologic evaluation of affected veterans and controls at the George Washington Univ. Medical Center, and a laboratory approach to investigate the pathogenesis of the proposed illness.

At the conclusion of Dr. Levine's presentation, Chairman Binns asked a general question about whether these particular neurological tests have typically not been found to be abnormal in GW veterans, and whether more dynamic challenge-like testing would be needed in order to reveal something, or had these tests shown something in GW veterans elsewhere?

Dr. White replied that all she could speak to was the cohort she studied, which was quite a bit larger than Dr. Levine's cohort. Dr. White's study tended to find an affect in quantitative continuous outcome measures more than normal/abnormal type studies. She thought a lot of what she saw was "preclinical."

Dr. O'Callahan said that, with respect to the electrophysiological measures, he thought that underlying preclinical damage to the CNS could be present without seeing effects on most of those evoked potential measures.

Dr. Levine responded that he was sure that was true, but that it could have been in all the groups.

Dr. Bill Meggs commented that one test found to be abnormal in organophosphate poisoned people – even after one acute poisoning – is pupillometry (the rate of change of the pupil area with time is abnormal). Dr. Meggs warned that some neurologists might shine a light in the eye, see restriction of the pupil, and conclude that the reaction is normal. He concluded that he thinks this addresses some of what Jim said; the gross exam may be normal, and unless researchers/neurologists look at some of these more refined tests they won't pick up the abnormalities.

Dr. Levine then asked if Dr. Meggs knew how long that effect lasts.

Dr. Meggs stated that such studies were done by Ishikawa in Japan originally, and he believes it's a permanent deficit that's seen.

Chairman Binns then told Dr. Levine that the Committee initially contacted him because of his very interesting paper on cancer rates in GW veterans. He stated that Dr. Kang would be presenting to the Committee the next day (Tuesday, September 16), but he asked if Dr. Levine could describe how that study came to being, and what the current status of it is, since he was the original Principal Investigator.

Dr. Levine replied that when he was at the National Cancer Institute, they had a program looking at cancer in AIDS patients, so he set up a matching program where he worked with states to take their AIDS registry and their cancer registry. He tried to match the people by name, age, birthday, social security number. He stated that this was all done in a "black box" which came out with matches of patients who were in the AIDS registry matched with their cancers. He had decided to work with Dr. Kang for a few years, trying to do the same thing with cancer registries matched with deployment registries. That was the origin, to take the same approach. Chairman Binns then asked why Dr. Kang is currently the PI, rather than Dr. Levine. Dr. Levine replied that he ran out of money and the CDC said they couldn't afford it anymore, so the VA picked it up.

Chairman Binns then thanked everyone for a very interesting and certainly sobering morning. On behalf of the Committee he stated that he appreciates all the good work that has gone into studying this very important topic, and that it was a great example of the very good use of the Committee's time to have everyone present at the same time together. He then adjourned the meeting for lunch.

The meeting reconvened at 1:45pm, and Chairman Binns introduced Dr. William Goldberg from the VA's Department of Research and Development.

#### **Update of VA Gulf War research**

Dr. William Goldberg

Committee Designated Federal Officer (DFO), VA Office of Research and Development



Dr. Goldberg began by welcoming everyone on the behalf of the VA. He then made note of the current 2008 portfolio for VA, which was distributed to all Committee members and available for the public. He added that the \$15 million that was contracted with UTSW was not included. He explained that, since the VA does not pick, choose, or control those projects they are not on its official Office of Research and Development (ORD) funded project list. He also noted that, copies of the 2006 and 2007 annual reports to Congress were available to anyone present. He explained that there is an annual report on all federally funded projects, including U.S. Department of Health and Human Services (HHS), DOD and VA. He added that Congressionally Directed Medical Research Program (CDMRP) projects were not (and would not in the future be) included in that report. He then told Dr. Haley that if he wanted to send him a list of ongoing projects and small descriptions that they could be inserted into the 2008 report when the ORD starts working on it in January. Dr. Goldberg announced that the ORD has one new project that has been selected for funding but it has not been started yet. He said he has not been seeing a lot of GW projects coming in under the normal submission process. Most of what had been coming in were projects related to Operation Enduring Freedom (OEF) and Operation Iraqi Freedom (OIF). Occasionally a GW project comes in, and Dr. Goldberg said that he does keep his eye out to make sure they do get counted if and when they come in the door as general research submissions. He added that there is no current ORD wide request for applications, since \$15 million has been contracted with UTSW. He said he would be happy to take any questions (about the program, or what's going on, or anything else).

Chairman Binns asked if there were any questions, and commented that he was pleased to see that Dr. Ronald Bach had a line item on the list for his follow-up work.

Dr. Goldberg stated that the follow-up project was in addition to his original study that was done as a service-structured project. He also noted that the follow-up study also has its own funding on top of what he originally received. Chairman Binns then asked whether Dr. Goldberg and the ORD had decided on a dollar amount for that yet. Dr. Goldberg apologized and said he would get that corrected and send it around to everyone. He said that in fact there was a decided dollar amount, and that the project was increased, but offhand he couldn't tell the Committee what the figure was.

Chairman Binns then commented that everyone would recall that Dr. Bach's original study was the very interesting study reported at the last meeting, related to coagulopathies. He said that it was very encouraging to see that even before that meeting Dr. Goldberg and his colleagues had identified this as a very promising area of research, and had agreed to fund follow-up work. Chairman Binns added that he also thought it notable that two of the VA researchers listed on the portfolio – Dr. Kang and Dr. Wong – would be speaking to the Committee the next day. Chairman Binns then asked if there were any other questions or comments regarding VA, then thanked Dr. Goldberg.

Chairman Binns then announced that the next speaker was scheduled to be Dr. Golomb, to speak about her Co-Enzyme Q10 therapy research project which had been funded under the CDMRP. However, due to travel complications, Dr. Golomb's presentation

was delayed until the next day. Chairman Binns then introduced the next speaker, the Reverend Joel Graves, a member of the Committee and a former GW veteran.

### **Environmental exposures during the Gulf War**

Rev. Joel Graves  
Captain, U.S. Army, Retired  
Member, Research Advisory Committee on Gulf War Veterans' Illnesses

Rev. Joel Graves spoke about his experience in the Gulf War, specifically on the illnesses he and his troops experienced in relation, he believes, with the Basra attack (See Appendix A – Presentation 6). During his presentation, Rev. Graves said that he wants the DOD to look at this incident more closely and validate the anecdotal evidence, as they did for the Khamisiyah nerve agent exposures. He would also like someone with the authority to ask the GAO to study this exposure incident. He would like the VA to help to increase awareness among Gulf War veterans and researchers about the Basra exposure. He would also like to see the Committee recommend and push for specific VX studies that look at effects and treatments, and hoped UTSW would take this on as well.

Dr. Melling, who works for the GAO, then commented that in order for the GAO to embark on any study it essentially requires a request from Congress, normally the Chair of a congressional committee, occasionally an individual Congressman or Senator. And he said he would be happy to share the names of a few contacts.

Dr. Meggs then asked if the alarms that were repeatedly going off during the GW were specific to nerve gasses or any other substances.

Rev. Graves replied that his unit had the standard issue chemical alarms. He assumed that the units around them also had the standard chemical alarms, but he noted that there were other coalition forces in the area – Czechoslovakia, Britain, and others – whose alarms went off, but that he didn't know what alarms they were using.

Chairman Binns apologized for the absence of Dr. Lea Steele, who has looked into what the chemical alarms can detect.

Rev. Joel Graves commented that he was a Nuclear, Biological, and Chemical (NBC) Officer, and claimed that the alarms would detect something like an aerosol spray blown downwind, because they are set up to capture substances other than smoke (i.e. vapors).

LTC Adam Such, a Committee member, noted that the alarms didn't have specificity, and were actually quite crude systems that relied on additional sampling. They gave false positives all the time.

Mr. Anthony Hardie then thanked Rev. Graves and pointed out that his presentation highlighted that in the years since the GW, the further governmental investigations of additional incidents of reported chemical exposures has largely – entirely – fallen away. He suggested that perhaps this would be a matter that could be referred to the Advisory

Committee on Gulf War Veterans (the other GW Committee) as well, to revive some of that research.

Chairman Binns then called on veterans from the Committee and audience to present any testimonials they might have regarding events they experienced which they associate with illness.

LTC Adam Such then noted that Rev. Graves referenced something called the Iraqi Study Group (ISG, also referred to as the Iraqi Survey Group) report, based on information from 2004 involving the discovery of chemical improvised explosive devices indicating loss of control over chemical munitions that were unaccounted for by ISG, American ground forces, the United Nations Special Commissions (UNSCOM), and the United Nations Monitoring, Verification, and Inspection Commission (UNMOVIC). LTC Such then stated that the anecdotal evidence presented by GW veterans after the war, though not corroborated by science at the time, was in fact being corroborated by Iraq's own admission, the UN's own admission, and evidence by U.S. presence on the ground; "we were finding sarin, cyclosarin, reports of VX – in terms of tons of it, in terms of how it was moved down along the front lines by the Iraqi units and their methodology for employment." There were a lot of chemical alarms going off at the beginning of the initial phases of the air campaign, and there were a lot of chemical alarms going off which were reported and then dismissed. Mr. Such then stated that it would have been completely possible that those explosions along the front lines and the decentralized use of chemical munitions by the Iraqi military would have lit off and have caused that exposure. LTC Such then claimed that the research of the ISG is showing now that the Mufana munitions plant may be far worse than the Khamisiyah one. He added that there's a lot of information now coming out, due to the U.S. occupation of the countryside, and digging through Iraqis' records themselves, that corroborates a lot of the anecdotal evidence. Mr. Such concluded by saying that there may be some stark points from an investigative standpoint that already exist that could then assist in a lot of the research going on right now in the medical and scientific community.

Anthony Hardie, member of the Committee and GW Veteran, said he wouldn't go into any real detail, but would list where certain incidents had occurred. His account follows: "Ras Al Mish Ab is a coastal area just north of Al Jubayl, it would have been sometime during the first 30 days of the war, so sometime between the 17<sup>th</sup> of January and the middle or so of February. It was marine central command forward. They were taking chemicals, we were just west of them. It was then confirmed (the British came and further confirmed it) and then the incident went away several hours later, but we had at least triple confirmation. Another incident may have taken place in Khafji, shortly after the marines had liberated the city after it was taken by the Iraqis – this would have been about the middle of February 1991. Late February to early March we would have been in an area just north of the Kuwait Bay, just west of Boubyan Island. There was an Iraqi unit that had been dug in there, and they had left, and I was doing some surveying for intelligence value of that area. The Iraqi unit had left in such a hurry that they left food on their plates, sleeping bags, personal equipment – which is pretty unusual for troops moving out to leave their personal equipment. And we noticed the distinct odors of

geraniums and wet/rotting onions or garlic. Those are characteristic of blister agents – Lewisite or mustard gas. While the damage could be immediate, the effects might not occur for as long as 24-48 hours later, but often 8-12-14 hours later, so a very small group of us there probably took the brunt of that exposure, staying in long enough to pull some items out. At least those three that I’m aware of, there may be others if I tried to recall.”

Mr. John Schwertfager, a GW veteran from the audience, and Vice President of the NGWRC, spoke about his experience in the first marine brigade – stationed “up to the left” of Anthony Hardie’s troops. Mr. Schwertfager attested to the chemical alarms that occurred as a result of incoming attacks experienced by his brigade. Mr. Schwertfager spoke of dead animals in Kuwait city that looked to have died of unnatural causes (“foaming at the mouth, no flies around them”). He also mentioned that he and his fellow troops were responsible for the clean-up of the Kuwaiti National Airport.

Mr. Richard Teele, who was with the Fleet Hospital 15 in Al Jubayl, Saudi Arabia , referred to his experience bringing in Seabees with the “purple shirt incident.” He was also a member of the hospital’s decontamination team, and carried a Chemical Agent Monitor (CAM – a detector for chemical weapons) that went off 22 different times while he was there. The first incident he experienced while in the area involved the detectors going off after a scud had been shot down over their heads. “This was the first time we were instructed to use our Mission Oriented Protective Posture (MOPP) gear, and as we were opening the packages of our MOPP gear it all fell apart – it was all dry rot. So we all had our gas masks on, but...we got there in January, and in the middle of February – after we had already had our canisters on our gas masks for over a month, because we couldn’t get resupplied, that’s when the chemical [scud explosion occurred]...it smelled almost like an onion smell in the air, but the gas masks didn’t help because the filters were totally done.”

Maj. Nichols then brought up Shays Committee hearing, and the two references that she feels will be important to validate with Rev. Graves’ information. “There was a Sergeant Gleeson, I believe his name was, with the marines, and they did a unit survey showing the percentage of marines from one unit that were sick. The second reference will be in Shays hearing with the VOX vehicle detection unit – Sergeant Grass, who also testified to the Presidential Advisory Committee. And also Major Johnson, I believe. That would correlate with this instance.”

Chairman Binns then called on Mr. Jim Bunker, who had planned to make a comment during the public statement session.

Mr. Jim Bunker, who was with the field artillery unit of the “Big Red One” stated that Rev. Graves came close to the same days he got sick. Mr. Bunker elaborated on his public statement (See Appendix B – Public Comment 1). In addition to what was written in the statement, Mr. Bunker mentioned that just before the 15<sup>th</sup> of March, several hours prior to his sudden onset of illness, his unit “blew up a big animal bunker just north of us.” The rest of his account is detailed in the public statement. Mr. Bunker also

mentioned the toxic chemicals that were sprayed on the troops' clothing, commenting that he and other troops would "drench" their clothing in these nerve-agent-like chemicals [organophosphates] and put them on immediately afterwards. He added that nobody in his unit used dog collars, though some other people did.

Dr. Meggs then asked about the "waxing and waning cognitive dysfunction" described by Mr. Bunker. Specifically, he asked whether the dysfunction is worsened by subsequent exposures (i.e. if he finds himself near someone spraying something or heavy exhaust fumes).

Mr. Bunker confirmed that he could not tolerate being near any kind of insecticide, pesticide, etc. He said that even his neighbor's citronella candles and tiki torches drive him indoors because he "can't be around it." He also said that he can't use bug spray, and that some perfumes cause reactions as well. In order to boost his quality of life and attempt to stave off bouts of dysfunction, Mr. Bunker takes multivitamins, Co-Enzyme Q10, vitamin B supplements, swims, rides an exercise bike, does physical therapy and stretching. Though this tires him out, he is now able to ambulate without crutches or a cane.

Chairman Binns then thanked Rev. Graves, Mr. Bunker and the rest for their courage and their presentations before introducing Dr. Robert Haley.

### **Update of UTSW Gulf War research**

Dr. Robert Haley

Director, Division of Epidemiology in the Internal Medicine Department at the University of Texas Southwestern Medical Center  
VA Dallas Healthcare System

Dr. Haley had no PowerPoint presentation. Dr. Haley first overviewed the original strategy of his research, which he broke down into 3 phases: an overarching, stratified random sample survey of GW veterans – mostly deployed but also non-deployed – designed to try to determine a case definition to be used in the future (e.g. for clinical screening, etc.). His research aims to look at risk factor modeling – both self-report risk factors, and, to the extent possible, to develop objective markers of risk (e.g. GIS modeling, using time and place for surrogates for different plumes and different exposures). His plan, originally, was to "also select a sub-sample of the approximately 8,000 respondents (participants) – all those who met any of the case definitions (that is, the ill veterans in the survey) – and then a random sample of the non-ill." From these participants, Dr. Haley planned to take blood samples, from which he would bank serum, plasma, and DNA. He planned to study paraoxonase and its genotypes and polymorphisms, and then to do a whole genome study. "The second phase, after conducting some pilot studies, was going to involve bringing in a set of the sick and the well to Dallas and to do a brain imaging biomarkers study, where we would develop a set of brain imaging techniques basically designed to go at what the symptoms are of the GW veterans – that is, things that would look at functional MRI (fMRI) of cognitive issues that veterans have (for instance, name-recalling problems, word generation

problems, attention concentration problems) and develop fMRI paradigms that hit directly at those symptoms. The idea is to present cognitive challenges that a sick GW veteran is unable to do, but that a well GW veteran *is* able to do, and look for different patterns of brain activation in the sick vs. well veterans.” Dr. Haley would also like to look at biochemical markers of brain cell dysfunctions, “e.g. using diffusion tensor imaging (DTI) – basically looking at white matter, looking at the wiring connections in the brain – to see if they might have been chemically damaged as has been shown in at least one study of the Japanese survivors to be abnormal. The third suggested phase of the study is a pre-clinical study attempting to find better information about the pathogenesis if the problem – or at least mechanistic studies – in mice, where we can use knockout technologies later to expose mice to some of the chemicals that have been implicated – e.g. pesticides, PB, and sarin – we’re working at Aberdeen proving ground through a CRADA with Aberdeen – they’ll expose the mice, and the idea is to then – we have 15 different protocols of looking at different mechanisms of brain function for which there is some rationale that these might be involved or relevant. At the end of a couple of years we would have survey data to define the problem epidemiologically, pulling together a lot of the observations that have come out before – we would have neuroimaging and biomarker study evidence available at the time that the preclinical animal study data becomes available. The idea would then be for everybody to look at that and see if we’re ready then to spawn some rational treatment protocols that would be based on the mechanisms that had been identified, to treat the issues that we’re finding in the clinical and survey data.

That was the original plan. The surprise and difficulty of this, besides designing and managing something complex like this, is that this had to be funded through a contract. Doing research by contract has been challenging, and this one has been particularly challenging, I think – and let me say that we are working very productively with our counterparts in the VA contracting process – this has been a process of moving forward and then stopping, then moving forward. Because of the contracting process there’s an urgency to get everything exactly right and have a perfect contract. Because if you don’t, the consequences are very damaging to contracting officers, technical representatives, etc. – if they make mistakes and let us do things that are wasteful or not authorized by the contract then the contracting people suffer. So, for the first 3 years of this, it was basically negotiating the contract so that it would be perfect. We didn’t understand that culture and were very frustrated. But now that we understand it, we see where they were coming from, and it was prudent. About a year ago we got the survey started first – actually we got a program management office funded first – we then got the survey funded, April a year ago and started the national survey. This has actually worked very well, up to a survey participation rate of about 60%. Part of the study called for us to obtain the address information on the approximately 15,000 sample members, from the IRS. There’s a law that requires the IRS provide locating information on any survey relating to chemical or environmental exposures – particularly that which involves veterans. So every study that has been sponsored by the government has used this, and it’s important because it makes the difference between a 50% and a 70% response rate, because it allows you to find people you would otherwise not be able to find. We were unable to get this – it was just tied up in round after round after round of tests and

negotiations with VA and the National Institute for Occupational Safety and Health (NIOSH) and with IRS. Last June our number of interviews just began plummeting because we had no more located veterans to find and still didn't have IRS data. VA was working very hard, and Paul Hutter (VA General Counsel) is one of the unsung heroes who has been aggressive and eager to help us, and I believe Han Kang was involved, and we finally got authorization and have just received the IRS addresses. Between June and now we have been finishing up the IRS effort and finally got the data and we should be back surveying probably in the next month from now. So we hope then to finish it up by perhaps December or January, and hope to have the full 70-75% participation rate.

Just about the time we melted down (in June, when interviews began plummeting, etc.), an interesting internet report came out by the Office of the Inspector General (OIG) of the VA. It was about the only other major research contract the VA had done. It was a large Vietnam Vets follow-up survey started in 2002, and it was a multi-million dollar survey funded by a contract, and finally the OIG investigated and shut it down, fired the investigator, and others. We all read this, and at the same time we had about 40 contract modifications that were needed to move various aspects that had just not gone anywhere between November and June, and the fault found by the OIG was that there was no overall project management – nobody whose job it was to make the project go. We realized that we were stymied for the same purpose, contacted Paul Hutter, and we asked for someone to be found that could manage the project and hold us all accountable, and they chose Shannon Novotny, who is in the Dallas Regional Office of the VA in Arlington. Shannon took over in June as the project overseer. Within a month, all 40 modifications had gone through, management was improved. Rick Thompson is now our Program Management Officer. I dwell on this because the contract management turns out to be the single most important aspect of this. The science is very important and complex, but we understand that; it was the management aspect that was difficult. Now that we have good management, our meetings are collegial and productive.

Let me now update you on what we've done with many of the suggestions you have made. One of the recommendations (particularly Carollee Barlow's) was that while we're collecting serum, plasma and DNA, the new thing is to collect RNA. We only collected 252 samples out of approximately 2,000 when you all met with us in January, and it turned out that at about that time blood collection stopped anyway – and had not started yet – because of issues over the Data Use Agreement (DUA) with DOD and VA. We were then able to master the technology, choose the right technique – we're going to use the PAX gene tube to collect RNA from blood (it stabilizes the RNA instantly). We've got the DUAs in place now, we've changed the consent form, we've got the contract modified, and we'll probably start the blood collection this coming Monday.

Case definition development was a big issue you raised. Lea Steele had a particular passion about that as we discussed at the last meeting. We were originally going to just use a factor analysis process that we've used before – that many have used – but apply it to a survey which we designed for this (which is important). We've since very thoroughly studied other alternatives for mining the data, coming up with a case definition and validated it. Since the sample is fairly large – approximately 8,000 – we've divided the

sample into 3 random thirds, instead of random halves, so that we can explore and develop on the 1<sup>st</sup> third, validate on the 2<sup>nd</sup> third, and then if there are modifications that come out of the validation we can then carry that out and validate it out again on the 3<sup>rd</sup> third. We think this is very important because in our earlier studies we've found that we could get most of the way with factor analysis, but when you try to validate it you find some important nuances, and every time you come up with something new there is the danger that this new phenomenon may either be real or the danger may be that it may be over-fitting to sample variation. The larger the sample, the less likely that is to be true, but now we will have a third sample (two shots) to verify, so we think we will be able to get it right. In addition to factor analysis we have been studying cluster analysis and a thing called correspondence analysis. These will be three different ways of exploratory data analysis – of viewing the data – trying to identify what are the unique clusters of symptoms that would identify the illness, and how do these differ between the deployed and non-deployed populations? In the preliminary work we're actually starting running these first on the study we did on the SeaBees (a Dallas VA study we did). We're running these initially to learn about the techniques and develop some hypothesis for our original studies. Then we will validate on the 1<sup>st</sup> third, then the 2<sup>nd</sup> third and so forth. What we're finding is that there does appear to be an actual data cut point in factor analysis, which we think we're seeing in cluster and correspondence analysis as well, is that it looks like we're actually going to come up with a data-derived rational cut point that defines the sick group. If that is true, I think it would be a big advance.

We're also now working on looking at the prevalence of the different syndrome groups. We're looking at our original case definitions – remember there were 3 major syndromes – but we're also looking at the Steele definition - the Kansas definition, and at Fukuda's CDC definition – to compare those, and what's their overlap. What kinds of people are included in one but not the other? We're estimating the prevalence of these using SUDAAN (a software package that estimates standard errors correcting for sample design). So we'll look at the prevalence and then be doing multivariate modeling of these definitions against risk factors. We're also looking at risk factors and exposures in the Gulf, self-report data as well as various plumes superimposed on the GIS data, as you heard earlier this morning. I think one of the most interesting analyses is to take a given case definition, analyze jointly – in a multivariate fashion – self-report risk factors, and the Khamisiyah 2000 plume. There was also a Lawrence Livermore plume which actually the GAO reported as much more credible, so we're going to compare those 2 plumes and we're trying to develop a GIS model of the earlier exposures – earlier in the air war (the Mufana and Samara exposures) that we think, from looking at the data, are probably more likely to be responsible for any sarin-related illness. We will have variables that represent each of these plumes. There are actually different levels of exposures for the Khamisiyah and Lawrence Livermore plumes, and we will do multivariate modeling against the various case definitions and see (in a multivariate model) which one of the plumes explains the cases better, to see which one is a better predictor. For every sample member we have their unit, their UIC, their MOS (occupation), demographic variables and so forth, and we also asked them if they ever left the main body of their unit, then went in and got supplementary information about where they were (thus correcting some of the UIC misclassifications).



The discussion about the whole genome study was that we had originally decided to make this matching efficient – to take all the sick guys (1,000-1500 of those) and only a random sampling of well guys (because there would be 6000 or so of them, and taking data from all would be wasteful). But there was a very strong argument made in the subcommittee to get blood, DNA, etc. on all 8,000 participants. It's going to be all we can do to get all the 2,000 samples we originally intended to get within the next 9 months, when this contract runs out, but in the interim we are developing a proposal to put through the peer review group of this study to add on the other 6,000.

The neuroimaging study was delayed for a long time, because this study involved a number of techniques and different types of assessment. During the negotiation process, due to the complexity of the study, it got divided into 19 different studies/contracts. Thus they were funded one at a time over a period of 9 months. UTSW invested \$1.5 million into the pilot studies that were not funded under the grant. As of June 3<sup>rd</sup>, the whole thing is funded, the pilot studies got done. Three weeks after that we started our first “dress rehearsal pilots” and finished those by the end of June. In the middle of June we started working through the “focusing study” which we are currently halfway through. We will be doing the different syndrome studies in different phases. Hopefully by January we will have analyzed those data and will know what this protocol is finding. We will then hopefully be able to cut the protocol down according to what is useful and what is not.

Adding additional hypotheses in the biomarker aspect was an additional recommendation. We have negotiated a deal with the laboratory at Louisiana State University (LSU) looking at squalene antibodies, so we are collecting samples for them. We are looking at immunologic parameters to do on the samples as well. There may also be a way to look at DU as a probable cause. DU has been a problem because the assays for DU have been very insensitive. The Defense department has been very active looking at people who have retained shrapnel wounds. There's lab in the UK and we're talking with that group to possibly work with them. I don't think personally that it is likely, given the distribution and properties of DU...but nobody can know what is true so we want to include everything that anybody has suggested that can be measured.”

Dr. Haley then called on Rev. Graves, who asked whether new measurement equipment can detect DU particulates in the brain. The question was based on his premise that, “if you're driving through the battlefield and are inhaling the smoke of burning vehicles that have been hit with DU rounds, then you probably have DU particulates in your lungs that, under conditions of high stress, may cross the blood brain barrier (BBB).” Dr. Haley responded that this is not something that can be measured in living individuals, though potentially studying brains of deceased veterans could reveal such information. However, Dr. Haley referenced the UK physics group's current assay which is apparently sensitive enough to study the decay of DU in the body, even after 17 years.

Dr. Haley then addressed the plan to have 15 neuroscience groups conduct pre-clinical studies in mouse models for exposure to pesticides, PB and sarin. Since the research groups were reviewed, the first 3 have been funded, and 9 “are beyond dispute” (i.e. have

been approved for funding). Three more are currently being reviewed, with minor modifications to be made. There are four that are being re-designed or re-drawn, and will be reviewed with Dr. Gilman – Chairman of the review Committee.

Dr. Haley has also expanded the toxicologic animal study component. Since the review committee suggested that research be done into prolonged sarin exposure (6 months, vs. 3), Dr. Haley has added additional batches to his existing ones, where behavioral testing will be conducted at 6 and 12 months (with 12 months being half the lifespan of a mouse).

Dr. Haley has also cut back the neuroimaging component, so that it will be a pilot study to look at the feasibility of various neuroimaging techniques he would like to do later (after the first year of pilot studies).

Dr. Haley also noted that his contracting office has tripled in size over the past 4 months, and that his team is very excited and optimistic.

Chairman Binns then called for questions.

Dr. Dedra Buchwald first asked what Dr. Haley was predicting regarding his regression models. Dr. Haley responded that he would be looking at linear models, at the multi-variate association of multiple risk factors with a dichotomous outcome.

Dr. Buchwald then confirmed that he is actually looking at cross-sectional data, without making predictions. She then commented on the importance, potential influence and inquired about measurement of psychosocial variables (e.g. catastrophizing, motivation, self-efficacy of veterans being studied) in his neuroimaging studies, citing relevant findings of Dr. Clauw and Dr. Richard Gracely. Dr. Buchwald also expressed concern over the selection of participants in the control group(s). She then asked who he drew his controls from. Dr. Haley responded that his controls were both deployed and non-deployed veterans. A discussion regarding methodologies then resulted.

Dr. Buchwald, drawing on Dr. Levine's earlier comment, asked about Dr. Haley's thoughts regarding the possibility that the "trigger" could have happened prior to the war (e.g. during stressful pre-deployment training or vaccination in the U.S.), and what implications this could have on his study findings, given his chosen control group.

Dr. Haley agreed that "the control group should be identical to the cases, except that they do not exhibit the disease, and this is what we are trying to do."

Dr. Clauw then commented that this is not really what Dr. Haley is doing. Instead, Dr. Clauw argued, Dr. Haley is taking asymptomatic individuals and comparing them to symptomatic individuals.

Dr. Haley replied that the case definition is symptomatic, and so being a non-case means you're non-symptomatic. So he stated that for a case you want to pick a representative

sample of the symptomatic, and the controls – as Dr. Clauw pointed out – would be the asymptomatic individuals.

Dr. Clauw disagreed. He claimed that all of these conditions – like fibromyalgia (FM) and chronic fatigue syndrome – are characterized by abnormalities in the same imaging studies that Dr. Haley is doing in GW veterans. In Dr. Clauw’s understanding, Dr. Haley is doing neuroimaging studies to infer etiology of the underlying symptoms. But, he argued, if one wants to infer etiology of the underlying symptoms one must have symptomatic individuals who have the same symptoms as the people being studied – those who didn’t get deployed to the war. Dr. Clauw then went on to say, that for any symptom cluster present in a GW veteran he could find thousands of people in the U.S. that have the same symptom cluster but who were not exposed to sarin, unless sarin is leaking out into the general U.S. population. Dr. Clauw explained that when he does an imaging study and he’s trying to figure out how pain processing is different in someone who has FM compared to a control, he’s not trying to look at the trigger for FM, he’s trying to look at the difference in pain processing in FM and pain processing in controls – so he can use asymptomatic controls. But he points out that Dr. Haley is trying to use such studies to infer etiology.

Dr. Haley then denied that he was in fact inferring etiology from his studies, but Dr. Clauw disagreed. Dr. Clauw then cautioned – in line with Dr. Buchwald – that there are a plethora of things that affect neuroimaging, especially the very sensitive types of neuroimaging that Dr. Haley is using, that are not being controlled for in Dr. Haley’s studies.

Dr. Haley admitted that “imaging by itself isn’t going to infer the etiology” and denied that he had ever tried to suggest otherwise. He then stated that “what determines etiology is the inference from the way you selected the sample.”

Dr. Buchwald then pointed out that one can’t infer etiology from a case-control study. “I think the difference that we’re talking about is, if you’re looking at the difference between someone who has GW syndrome and not GW syndrome and all you want to see is whether the brain looks different, then your cases should be asymptomatic people. But if you’re looking for what the trigger is (and you can’t talk about etiology), then you have to separate them on the trigger. If I’m making sense, either they experienced the trigger or they didn’t. What I was trying to say in my original comment is maybe the trigger occurred in boot camp, or maybe it occurred overseas.”

Dr. Haley then argued that this is an epidemiological question that can be resolved by asking when the veterans got sick. Dr. Buchwald corrected him, stating that those questions address when the onset of the illness occurred, not when the exposure could have occurred (which could be prior to the exhibition of symptoms).

Dr. Haley then suggested that the solution would be to compare imaging in those who “had an epidemiologic exposure” to those who didn’t, arguing that Dr. Buchwald and Dr.

Clauw disagree. Dr.s Buchwald and Clauw claimed they do agree, and Chairman Binns interrupted to call on Dr. Nettleman.

Dr. Nettleman then asked why Dr. Haley had chosen to do brain imaging. Dr. Haley responded that “what we have is a group of veterans who have an undiagnosed/unrecognized illness,” that is not recognized as physical in origin. Therefore, he believes that “it is most important to try to identify if there is an organic dysfunction in them.”

Dr. Nettleman then asked if Dr. Haley is looking for a “biomarker, or an imaging marker, for the syndrome complex.” Dr. Haley stated that one of his “objectives is to find a set of objective markers that identifies GW Illness as an objective disease that can be objectifiably diagnosed.”

Dr. Nettleman then asked whether, if he were to find the marker he is looking for, how he would know that it was not simply fatigue or something specific to GW illness. Dr. Haley responded that looking at GW veterans is the priority, and that assessing other diseases would be secondary.

Chairman Binns then said that “we have looked in the past at relationships between GW syndrome and CFS, and in essence what we have found is that some studies find similarities and others find differences.”

Dr. Meggs then commented that a CDC study from 2005 reports that everyone in the US contains measurable levels of organophosphate insecticides, herbicides, heavy metals, and a whole host of these chemicals – that everyone in the country is exposed.

Robert Walsh from the NGWRC made an inquiry about Depleted Uranium (DU), and how a study of that cohort could be done to detect DU in urine. Dr. Haley responded that he believed this information could be gathered by conducting a simple 24 hour urine sample.

At 3:40pm Chairman Binns called for a break and commented that the conversation regarding Dr. Haley’s research could be continued at the next Committee meeting in Dallas in February.

Dr. White reconvened the meeting at 3:55pm and introduced Dr. Mitchell Wallin.

### **MS and Gulf War veterans**

Dr. Mitchell Wallin  
Clinical Associate Director, VA MS Center of Excellence East-Baltimore  
Associate Professor of Neurology, Georgetown University School of Medicine

Dr. Wallin provided an overview of Multiple Sclerosis (MS), including evidence of potential environmental risk factors, followed by an update of his current study of MS in

Gulf War veterans (See Appendix A – Presentation 7). The study, which is in its first of three years of funding, hypothesized that deployed GW veterans would be at increased risk for developing MS compared to non-deployed veterans. The study's secondary hypothesis was that the in-theatre exposure characteristics of deployed GW veterans will be associated with an increasing risk for developing MS. Dr. Wallin concluded by briefly overviewing other studies – including case-control studies and environmental survey studies – that the Center of Excellence is conducting to assess the risk of MS in GW veterans.

Steve Smithson asked whether Dr. Wallin looked to see what other conditions the study's service-connected veterans with MS might have, to identify any correlations. Dr. Wallin replied that he does plan to collect information on any other service-connected conditions which the veterans may have.

Dr. Nettleman then asked whether there had been any research to date on the micro-environment of the gene (contrasting this with external environmental factors). Dr. Wallin responded that this is currently a hot topic and that there is currently a lot of epigenetic research being done to investigate how things like Vitamin D can change signaling in the immune system, particularly in mouse models (including in-utero exposure).

Dr. White then asked Dr. Wallin what he was looking for in his MRI reviews (e.g. white matter lesions), pointing out that there are many GW veterans that have white matter lesions but do not have clinical MS. Dr. Wallin replied that he is using the MRI data predominately for diagnosis, particularly in the longitudinal study that the Center is conducting, but noted that MS is still a clinical diagnosis. Dr. Wallin added that all participants in his study must first make it through the initial VA service-connection screening, and that his research team is also able to confer with colleagues in the MS clinic network that is set up throughout the country.

Dr. Haley commented that in his GW ALS study, 2/3 of the patients who eventually were diagnosed with ALS had exhibited symptoms of GW illness immediately upon returning from service (compared to the 20-25% of the “general group” of returning GW veterans who exhibited immediate symptoms). He then postulated that there might be an etiological link between the disease processes of ALS and GW illness. Dr. Haley then asked Dr. Wallin if he was able to get evidence of whether the veterans in his study were ill when they came back. Dr. Wallin replied that the nature of the service-connection process forces an individual veteran to show when their MS started. It has to be during active duty, or up to 7 years after. Dr. Wallin said he looks at this data of when the symptom(s) started, in the context of each participant's medical history/chart. Dr. Haley, noting the sometimes subtle onset of MS, then suggested the need for two variables: 1) the status of the veteran when s/he first came back from the war, and 2: separately track what/when appeared to be the onset of the patient's MS (e.g. optic neuritis, etc.).

Maj. Nichols then commented on the preponderance of eye problems in GW veterans, and expressed concern regarding many veterans' lack of access to eye care. She then

called for more research into GW veterans with eye problems. Dr. Wallin replied that one of the things MS Centers are trying to do is provide at least one multidisciplinary MS center within every Veterans Integrated Service Network (VISN) that can actually serve these needs. In VISNs 1-11 there are at least 1, and sometimes 2 or 3, MS Centers that can actually serve the needs and make referrals to subspecialty clinics if a veteran has a symptom that looks like MS. In response Maj. Nichols expressed concern over those veterans who have symptoms but are not diagnosed, once again pushing for researchers to design a study that could at least perform evaluations on GW veterans experiencing eye problems. Dr. Wallin replied that there is “a move afoot” to get veterans seen within 30 days in clinics.

John Schwertfager, GW veteran, expressed concern about his eye problems (he is developing glaucoma in both eyes but has not been diagnosed and is not service connected). Furthermore, he reported having other undiagnosed, non-service connected veterans come to him with similar symptoms, who he can only refer to homeless shelters due to lack of other options. He then asked what he could be doing for these veterans (he deals with veterans from the Ohio and Indianapolis regions). Dr. Wallin replied that he and his fellow veterans should be getting care, and that it must be dealt with on a case-by-case basis, working with each veteran’s specific VA to identify if there’s a service-connection barrier. Mr. Schwertfager then claimed that the problem is nation-wide, Dr. Wallin denied that this is the case in DC. Maj. Nichols then expressed her concern that valuable data is being lost that could otherwise be used to support research and get treatment for veterans – who could then re-join the workforce.

Chairman Binns then asked Dr. Haley if eye exams were going to be included in any part of his study. Dr. Haley replied that he would not be doing an ophthalmologic exam, but that he will be conducting a “vision fMRI study” where objective evidence about visual and visual cortical activity would be obtained.

Mr. Bunker then pointed out that Dr. Wallin’s end date criteria/cutoff point of July 31, 1991 – which is the same criteria used for his ALS GW study – “leaves out in the cold” a lot of the veterans who were still in the desert in Kuwait, doing a lot of the clean-up, and who were therefore still being exposed to many of the hazardous environmental factors being studied in the rest of the veterans. He asked why the end date could not then be extended in this MS study to a point at which the clean-up was done. Dr. Wallin responded to this a bit later, inviting everyone present to contact him if they had any alternative definitions for “Gulf War Veteran.”

Maj. Nichols then noted that the drug insert for the anthrax vaccine lists a possible connection between the vaccine and contraction of MS, and asked whether Dr. Wallin was connecting with the DOD vaccine injury clinic at Walter Reed, in order to pick up any of those cases. Dr. Wallin responded that good vaccine data on the GW veteran cohort (including the existing registries) is lacking. He added that he is connecting with the DOD, and that there are better records being kept on vaccines given for the current conflict than there were in the 1<sup>st</sup> GW (and he specifically named a new collaborator, Chris Jankowski, who apparently runs the occupation health clinic and residency at

Bethesda). He said that he would be looking at these service-specific reports (on troops in the current conflict) being kept at the surveillance center at Walter Reed.

Mr. Schwertfager then asked what is being or could be done to catch and treat the many symptomatic but undiagnosed veterans who exist nation-wide, many of whom have become disillusioned by – and thus left – the VA, only to wind up on the street. Furthermore, Mr. Schwertfager wanted to know what could be done to prevent this pattern from continuing. Dr. Wallin replied that in the MS system, he and his colleagues have tried to create hub sites for MS Centers of Excellence with multidisciplinary centers within each VISN, so that veterans can go to their particular VA and get a second opinion and a work-up. He cautioned that some of the drugs they use for MS have side-effects, so someone with MS wants to be sure that their diagnosis is real. In the ~3 years the Centers have existed, they have developed a system of care that involves a system of referrals within every VISN (much like the Spinal Cord Injury – SCI – handbook), which is on their website.

Chairman Binns then thanked Dr. Wallin and pointed out that this study was in response to a recommendation that the Committee made in 2004 to study other neurodegenerative diseases besides ALS. Chairman Binns hopes this example will lead to a greater awareness within the VA system. Dr. Wallin then offered his contact information for anyone wishing to make suggestions regarding how “Gulf War Veteran” should be defined (see above).

Chairman Binns then acknowledged that the schedule had allowed for public comments throughout the day’s presentations, and invited anyone with remaining comments to come forward at this point.

### **Public Comment – Day 1**

Dr. Jim Baraniuk began by thanking the Committee for the support he had received through the CDMRP. He then took a survey of how many people present were in the GW theatre and how many were volunteering for the CDMRP studies, then encouraged healthy volunteers to join. Chairman Binns thanked Dr. Baraniuk and encouraged anyone with experience recruiting veterans to talk with Dr. Baraniuk and his colleague about good techniques, and to “help them get the best study they can now that it’s been funded.”

Maj. Nichols then came forward with two final questions regarding the need for research into other parts of the body (aside from the brain). She first asked that future GW illness research surveys include *standardized* questions regarding demographics – what unit each veteran served in, what type of job each veteran held, the veterans’ location in theatre. Maj. Nichols’ was also concerned about early deaths among GW veterans – including those due to cardiac problems (which was Maj. Nichols’ specialty in nursing) and deaths at home potentially attributable to suicide. Maj. Nichols re-iterated her

concern about eye problems, and also brought up concern over dental problems (teeth breaking off and fillings, crowns falling out, often without pain).

Chairman Binns thanked Maj. Nichols and all of the presenters and then called the meeting to a close.



## **Day 2**

Chairman Binns began the second day of the meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses at 8:30 am. The meeting was again held in Room 230 at the Department of Veterans' Affairs, 810 Vermont Avenue, NW, Washington, D.C.

Chairman Binns personally welcomed Capt. Melissa Kaime from the CDMRP, which is at the DOD and is engaged in researching treatments and diagnostic markers for GWI. Chairman Binns noted that the program has funded more pilot studies of treatments than had been approved in the previous 16 years of GWI research. Chairman Binns commended it for being exactly the type of program that the Committee had been urging the government to adopt over the last several years.

Dr. White then formally introduced Capt., Dr. Kaime.

### **CDMRP Gulf War program update**

Capt. Melissa Kaime  
Director, CDMRP  
Captain, Medical Corps, United States Navy (USN)

In her presentation (See Appendix A – Presentation 8), Capt. Kaime gave an overview of the CDMRP, highlighting how it differs from other funding agencies, who it partners with and how grant funding is managed. Capt. Kaime then provided a synopsis of the congressional appropriations for the CDMRP's Gulf War Illness Research Program (GWIRP) in 2006 and 2008. Capt. Kaime then provided overviews of the current projects (funded in 2006) which include studies on pathobiology, treatments, and diagnostics/biomarkers – several of which are being conducted by Committee members. Capt. Kaime then highlighted the GWIRP priority areas and the 2008 "Investment Strategy" (e.g. what different types of research proposals were being considered for 2008 funding). Dr. Kaime named some of the integration panel members responsible for reviewing the 2008 GWIRP proposals, several of whom are also Committee members. Capt. Kaime concluded by encouraging people to visit the CDMRP website, where approved project abstracts and resulting research publications can be viewed. Dr. Kaime then invited questions.

Dr. Golomb, who has been funded by the CDMRP, thanked Capt. Kaime for the opportunity she and other VA physicians had been given to conduct research in hopes of more effectively treating GW veterans.

Dr. Nettleman, who sits on the GWIRP integration panel, noted that – of all the panels she is a member of (including several NIH study sessions) – the experience of having advocates be included as members of the GWIRP panel made the review process one of the most useful she had ever been a part of.

Dr. Sullivan, who was funded by the CDMRP in 2006, also thanked Capt. Kaime for the opportunity to conduct her research regarding pesticide exposure in GW veterans.

Chairman Binns then thanked Capt. Kaime after pointing out that the CDMRP has the advantage of being open to all researchers (e.g. one award went to a VA researcher, another to a military researcher), including international researchers.

Chairman Binns then briefly introduced Dr. Han Kang, prior to his formal introduction by Dr. White.

### **Washington WRIISC research update**

Dr. Han Kang

Director, Environmental Epidemiology Service of the Veterans Health Administration, and

Director, War-Related Illness and Injury Study Center at the Washington DC VA Medical Center (WRIISC-DC)

Dr. Han Kang first presented an overview of three of his studies at the WRIISC-DC, beginning with a presentation on his study of cancer prevalence in GW veterans (See Appendix A – Presentation 9). After Dr. Kang's introduction, he called on co-investigator, Ms. Shannon Barth, MPH, to present the findings from their 13-year follow-up study of mortality among US GW veterans (See Appendix A – Presentation 10).

After Ms. Barth's presentation, Dr. White asked for the mean and range of the age of the GW veteran population when the data was analyzed, thinking in terms of the neurological outcomes. Ms. Barth did not have the exact figures, but estimated that the veterans were in their 40s, on average. She added that they used the veterans' age of entry into the study (13 years prior to the follow-up study being reported in her presentation). Ms. Barth said that she could find the figures for Dr. White.

Dr. Golomb then asked if there was a reason why the research team chose to focus on just two exposures – exposure to oil well fire smoke and exposure to nerve gas at Khamisiyah, but didn't choose to focus on other exposures which have been linked to increased risk of health problems, such as PB, pesticides, or multiple vaccines. Ms. Barth replied that the research team already had the oil well fire smoke and Khamisiyah data from Dr. Tim Bullman's previous study. Dr. Kang replied that he does not have data for PB use among all 700,000 individuals. Dr. Golomb then commented that there is high expectation for misclassification bias (based on uncertainties in the plume model and possibilities of exposure to nerve agents from other events) even for the official Khamisiyah data they used. Dr. Golomb emphasized that officially sanctioned exposure data are not necessarily superior to self-report data. Dr. Kang then said that he would be eager to apply any other existing exposure data to his mortality outcome analysis. Dr. Golomb then verified that Dr. Kang did not have self-report data on exposure for all 700,000 individuals in his study.

Dr. Golomb then expressed two concerns with the interpretation of Dr. Kang's data. She first questioned the statistical significance of the association found between oil well fire smoke exposure and increased brain cancer mortality risk, noting that the confidence interval (CI) of 0.998 indicated a 5% possibility that this outcome could happen by chance – many people would characterize as of borderline (not statistical) significance. Secondly, Dr. Golomb brought up her concern regarding accurate comparison of mortality in GW veterans relative to the selected control group. Dr. Golomb used the Sato anthrax vaccine study as an example to point out that veterans selected for deployment are a far healthier group than those non-deployed (i.e. with fewer of the other co-morbidities, concurrent medications and risk factors for many adverse outcomes). This she referred to as the “healthy warrior” issue. Dr. Kang acknowledged this limitation that their study compared deployed GW veterans (who may have been more healthy prior to deployment) than controls (who presumably may have been less healthy).

Dr. White then asked what the disorders included in the digestive diseases found to have been associated with increased death of female GW veterans. Ms. Barth replied that these included anything within the digestive disease ICD-9 categories. Ms. Barth said that, once broken down, the highest subgroup in their study cohort, i.e. those diseases which resulted in statistically significantly higher mortality, were alcohol-related chronic liver diseases. Dr. White also commented on the finding that married female GW veterans had increased risk for suicide, and Ms. Barth clarified that this meant the women were married at deployment, and that their research group had no data on their marriage status at time of suicide. Dr. Sullivan then asked for the total number of suicides in women. Ms. Barth replied that she would have to find that information and provide it later.

Dr. Meggs then commented on the likelihood of/possible relation between increased risk of alcoholism (and increased risk of alcohol-related liver disease) contributing to the increased risk of suicide, since alcoholics have an increased suicide rate and an increased risk of depression.

Chairman Binns thanked Ms. Barth for her presentation.

Dr. Kang then introduced Ms. Jessica Maillard, MPH, who helped conduct the research group's recent study on cancer prevalence in GW veterans (See Appendix A – Presentation 11). This study drew on data from dozens of state cancer registries, and the results were still being analyzed at the time of presentation. At the conclusion of Ms. Maillard's presentation, Dr. Kang called for suggestions, particularly on how the research group could analyze the data.

Dr. Golomb then brought up the “healthy warrior” issue again. She noted that individuals with diabetes (who would be selected away from deployment) have a higher risk of subsequent development of cancer, and asked whether Dr. Kang's research group would have a way to control for the deployed GW veterans lower likelihood of developing cancer for this reason. Ms. Maillard replied that she was hoping that the non-deployed veterans would be a good control group, and that the matching process would work well.

Dr. Golomb interjected that she did not think non-deployed veterans were a good control group.

Dr. Golomb also suggested that Dr. Kang's research team look at the age of onset of different cancers in different groups, and to see if there is a shift in trend of age of onset. Ms. Maillard said that the main age variable of interest would be the diagnosis age. Dr. Golomb encouraged using this as a point of outcome. Ms. Maillard noted that another planned analysis was to create graphs with time on the x-axis, to see if any spikes in cancer diagnosis appeared during the GW. She did note that many cancers have a longer latency period than even ~17 years (the current time passed since the GW), but that time-trend graphs would be part of the analysis. Dr. Golomb said that it was a different question, but also an important one, to see if there is a shift in average age of onset, relative to the average age of the population.

Dr. Nettleman then commented that she found both studies interesting, and asked if there was information on smoking status in deployed versus non-deployed GW veterans. Ms. Maillard did not have information on that at the time, but said that, just from looking at preliminary data, smoking status was going to prove to be a big issue. Dr. Nettleman then said that she accepts what Dr. Golomb has said about the "healthy warrior" effect, but she does not think that it can be used as a general rule to always say that mortality rates found in deployed GW veterans will be automatically lower than in non-deployed veterans. Dr. Golomb then stated that her point was that the results can't be interpreted as a result of this confound. Dr. Nettleman then said that results could be interpreted (i.e. cancer is lower in population X than in population Y), but that causality could not be inferred. Dr. Nettleman added that this should lead to more detailed studies where one could potentially adjust for a variety of factors that can't be controlled for in the huge population-based data, which she noted are quite valuable. The discussion concluded by Dr. Nettleman noting that both types of studies (small studies where causality can be inferred, and larger population studies which can't as easily control for all variables) have their limitations, but that both are absolutely critical.

Dr. Sullivan then noted the differences in dates when diagnoses were first and most recently available from state cancer registries. She then asked if some of the states with older "ending year" dates would be updated. Ms. Maillard replied that this was the goal when the research team set out, and that Maryland (the state with the oldest "ending date") was the first state in which the linkage was performed (this was done around 2002). Ms. Maillard said her team had contacted Maryland to update their data, but they have been having some well-publicized issues and are not currently offering data to researchers. Dr. Sullivan followed-up, asking if efforts would be made to update some in the older state linkages. Ms. Maillard responded that their current study is in the analysis phase, so they would unfortunately not be able to go back at this point. Dr. Sullivan was concerned that people were being missed and wondered if a follow-up study including recently added individuals from the updated registry. Ms. Maillard said that she is aware that the study is missing people, and that her research group has devised some methods to control for those differences, taking into account starting, ending and total year figures as

variables in the model to try to prevent skewing as much as possible. Ms. Maillard said there was currently no plan to do more data collection.

Chairman Binns then commented on the intent of Dr. Kang's research team to combine ground forces (army and marine) and compare them to combined non-ground forces (air and navy). Noting that ALS is a completely different disease entity than cancers, he recalled that the previous day's presentation on ALS found elevated rates of ALS in the air force and army, and whereas the low rates were in the marines and navy. Had they chosen to make the combined grouping outlined in the study presented here by Ms. Maillard, those findings would have masked. Chairman Binns therefore suggested that Dr. Kang's research team consider looking at each branch individually as well, if they weren't already. Ms. Maillard replied that the four branches would be included individually in the initial Gulf/Non-Gulf comparisons, and that the combinations would occur later.

Chairman Binns then thanked Ms. Maillard for her presentation.

Dr. Kang then presented his longitudinal health study of GW era veterans (see Appendix A – Presentation 12).

At the conclusion of Dr. Kang's presentation, Dr. Golomb asked what the risk ratio was for mortality from alcoholic cirrhosis in the previous study. Ms. Barth replied that she had looked at this figure in women, and estimated that it was 1.5. Dr. Golomb explained that she was asking because she wanted to point out that cirrhosis and cirrhotic death is not just a function of alcohol use, and that pro-oxidant vs. anti-oxidant factors moderate how much the same amount of alcohol will lead to cirrhosis. Dr. Kang replied that their research groups had survey data, but no information from the entire 700,000 participants.

Dr. Meggs then commented that the question often arises as to whether there is a unique GW syndrome. Looking at Dr. Kang's data might lead some people to conclude that in fact there is no specific GW syndrome, that GW veterans just develop the same diseases as the rest of the population, but at an earlier age.

Dr. Kang then mentioned that in part of another study his research group conducted, based on the 1995 survey data – on which his team did factor analysis to try to identify individuals with a particular cluster of conditions. He stated that such findings support the basis for Dr. Levine's presentation the previous day. Dr. Kang continued, noting the existence of a small but prominent number of GW veterans who experience a particular cluster of symptoms (loss of balance, seizures, etc.) and he and other researchers want to see if there is a biological laboratory test that can support the self-reported symptoms. He mentioned that Dr. Levine had studied this and published results.

Chairman Binns then thanked Dr. Kang, reminding everyone that the Committee had requested that questions on multi-symptom illness were included in Dr. Kang's survey (which they had been). Chairman Binns also concluded that Dr. Kang's results were consistent with other studies which show that, while diagnosed conditions are somewhat

elevated in many cases, that the real difference comes in this undiagnosed group which we have all come to call Gulf War Illness. Chairman Binns commented that it had been very impressive to see the VA with this very large study validating the state and individual studies done elsewhere.

Dr. White then introduced Dr. Gudrun Lange, who then introduced her two co-investigators.

**New Jersey WRIISC research update**

Dr. Gudrun Lange

Director, New Jersey WRIISC

Professor, Radiology & Psychiatry at the New Jersey Medical School at the University of Medicine and Dentistry of New Jersey

Dr. Karen Quigley

Associate Director, New Jersey WRIISC

Associate Professor, Psychiatry at the New Jersey Medical School

Dr. Helena Chandler

Clinical Psychologist, Dept. of Behavioral Health, VA New Jersey

Research Scientist, New Jersey WRIISC

Dr. Lange thanked the Committee and then commented on the shift of the research focus of her group. She then commented on the unique position and important role WRIISCs could have in reaching out to and developing treatment and management programs for GW veterans. Dr. Lange then introduced Dr. Karen Quigley and Dr. Helena Chandler. Prior to presenting, Dr. Quigley mentioned the current status of her study, which is in need of funding. Dr. Quigley then presented work she had conducted with colleague Paul Leher looking at the possibility of treating GW illness with biofeedback (See Appendix – Presentation 13).

Chairman Binns commented that this type of treatment is part of a protocol developed at Stanford for that has been found effective in treating chronic pelvic pain syndrome.

Dr. Kaime then asked that, if the biofeedback sessions were being done with a provider, whether the control group also had access to a provider (i.e. how the presence of a provider was controlled for in the study). Dr. Quigley replied that participants in the control group did come in to see a provider, but would simply do normal breathing rate pacing with (not biofeedback). Dr. Quigley then said that the “stress eraser” component of biofeedback that takes place at home could potentially be introduced to the control group as well, though the methodology would have to be worked out.

Dr. Chandler then presented some preliminary results from a telemedicine prevention program for veterans with GW illness (See Appendix – Presentation 13).

At the completion of Dr. Chandler's presentation, Dr. Melling asked about the status of cognitive behavioral therapy (CBT) with respect to illnesses other than (and including) GW illness. Furthermore, Dr. Melling asked if there was objective, statistically valid, properly controlled evidence that shows CBT to be beneficial in the context of GW illness, or whether CBT was too subjective to measure in such a way. Dr. Chandler said that she and her colleagues, along with Ben Natelson, had been having interesting discussions regarding this. She noted that there have been studies, including a meta-analysis conducted in 2000, that showed an overall positive effect of CBT on a variety of physical symptoms (gastrointestinal, fatigue, etc.) but that there have also been studies not finding an effect. She noted that the British studies have generally produced more positive results regarding the effectiveness of CBT than American studies. Dr. Chandler also expressed concern about standardizing [operationally defining] CBT.

Dr. Golomb cautioned against drawing causality from simple associations (i.e. a directional relationship can't be drawn from the observance of two parallel trends). Dr. Golomb also noted that people who have fewer symptoms are more compliant, but that there is a large body of literature showing that less healthy people are less compliant. Dr. Golomb added that there are huge differences in mortality as a function of compliance; as people get more health problems they feel less able to direct their energetic resources toward compliance in a clinical study. She said that she wouldn't presume that the people who were more compliant had fewer symptoms because they were compliant, but that the opposite could be equally possible (i.e. people with fewer symptoms were able to be more compliant). Dr. Chandler agreed, noting that the current study is longitudinal, so that the researchers can do predictive analyses. She also pointed out on Slide 21 that the catastrophizers and the non-catastrophizers are starting at the same point. Dr. Golomb then stated that Dr. Chandler was only pointing out that the changes occur in parallel, not that one change occurred or in any way caused the other change. Dr. Chandler agreed, and said that was a direction her research needed to go in. She noted that her research group could use ICD-9 codes to characterize patients on that kind of symptom or illness severity as well.

Dr. Golomb then made a comment that, as Dr. Chandler pointed out, CBT is an "enormous grab-bag" and that there are studies like sleep hygiene studies that call themselves CBT studies but that are more behavioral, less cognitive. She expressed curiosity about the specific cognitive techniques used by Dr. Chandler and her team in the study. Dr. Chandler replied that she would try to write up the specifics well when publishing the results. She also added a cautionary note, stating that despite critiques of CBT, reducing cognitive and mental health stress will improve functioning in many patients. She admitted that this is only one piece of the GW or CFS, etc. questions but that significant results – i.e. improvements in quality of life – can be achieved.

At 10:45am Chairman Binns thanked the New Jersey WRIISC team for their presentations, and announced that the VA Secretary would be arriving at 11:00am. He then called for a brief break.

Attendees reconvened at 10:55am, and at 11:00am Chairman Binns introduced the Secretary of Veterans Affairs, the Honorable James Peake. Chairman Binns then announced the presentation of certificates of appointment to several members of the Committee. These certificates were presented by Secretary Peake to LTC Adam Such and Dr. Roberta White.

After the awards were presented, Secretary Peake addressed the Committee and others in attendance. He first stated that he would be present in November for the release of the Committee's 2008 report. He also announced that he had recently commissioned another committee to provide advice from a different perspective on the issues of Gulf War veterans. He advocated for putting the best science, understanding, and the right human dynamic behind the efforts to provide the best services possible to those veterans who served our country. He then thanked the Committee for their work.

Chairman Binns thanked Secretary Peake in return.

### **RAC Committee report update**

James Binns

Chairman, Research Advisory Committee on Gulf War Veterans' Illnesses

Chairman Binns then announced to all those present that the release date of the report would take place during a one-day Committee meeting on Monday, November 17 in Washington, D.C. (in the same location as the current meeting).

Dr. Goldberg then commented that this date coincided with the annual Neuroscience meeting, and encouraged people to take that into account when making travel plans.

Chairman Binns then announced that the Committee staff would soon be surveying the Committee members for their 2009 meeting date availability. Chairman Binns then proceeded to read a letter from Dr. Lea Steele (who could not attend the meeting), regarding her draft of the last section of the RAC report (the neurotoxicant section), covering PB, pesticides and nerve agents. In her correspondence, Dr. Steele explained that the draft was comprised of summaries and earlier drafts presented at previous meetings, but that this document represented the first full-text version of the contents. Per Dr. Steele's request, Chairman Binns asked Committee members to send comments to her at their earliest convenience, no later than Friday, September 26. Chairman Binns then thanked everyone present after receiving no comments or questions from the Committee members regarding Dr. Steele's request.

Chairman Binns then introduced Dr. Beatrice Golomb.

### **Update of recent GW research**

Dr. Beatrice Golomb

RAC-GWVI member



Associate Professor of Internal Medicine, UCSD

Dr. Golomb presented an update of recent research related to GW veterans' illnesses (See Appendix – Presentation 14. These studies included epidemiological studies of GW veterans, studies of similar illnesses in the general population, animal studies, and human studies.

At the conclusion of Dr. Golomb's presentation, Dr. White commented on the terminology used in imaging studies. Dr. White noted that when Dr. Golomb was summarizing the FM studies, there were magnetic imaging spectroscopy (MRS) differences in the marker between FM patients and controls. Dr. White saw this as an example of the many studies reviewed by the Committee that show differences between different kinds of cases or controls or symptomatic groups which use the words "loss" and "change" frequently. Dr. White believes this is an inaccurate and misleading way to talk about the differences being seen, because the direction of causality is not known. Dr. Golomb agreed, stating that her use of the word "change" simply indicated a difference between the patient and the control groups, but that what she had meant was "difference."

An unidentified audience member started to speak, but was asked by Chairman Binns to wait until the floor was opened for the public comments section, given the tight schedule for the day.

Dr. Nettleman then commented on hospitalization, and noted that she could not send veterans to the hospital for many of the conditions from which they suffer (e.g. skin conditions, cognitive disorders, fatigue). She then noted that the fact (presented by Dr. Golomb) that hospitalizations were not common was perhaps not a compliment to the U.S. health system, since hospitalizations should be for acute self-limited illnesses, and therefore many individuals with chronic illnesses become disenfranchised. Dr. Golomb agreed that looking at hospitalizations doesn't reflect the spectrum of illness that individuals experience.

Chairman Binns then opened the floor for the public comments section, and called on Mr. Jim Bunker of the NGWRC.

### **Public Comment – Day 2**

Mr. Bunker stated that, after listening to the two days' proceedings, he felt that the most urgent need was for a standardization of criteria that defines who should be considered a Gulf War veteran, where the control groups are drawn from, and other veterans to help eliminate issues such as deployment stress and war. Mr. Bunker detailed his criteria for who should be considered a GW veteran, stressing his concern that veterans who entered the theatre after July 31, 1991 – including those who were responsible for cleaning up just after that date – are currently not eligible for service-connected care through the VA. Mr. Bunker also mentioned groups he felt should be considered for control groups (as veterans deployed to what he considers similarly stressful, hostile environments), including GW era veterans sent to Korea, Guam, and Panama. He cautioned that any

controls selected from these zones should be screened out if they had been in the Gulf prior to 1996, when the DOD changed a lot of rules and protocols regarding pesticides and other chemicals being used. He said these controls could be obtained from the DOD's unit manning reports. Mr. Bunker also encouraged the group to look at the group of veterans currently in OIF, because, he stated, that for the first year they went through the same deployment and battle conditions that the GW veterans did, but their environmental/toxic exposures due to nerve agents and oil wells would not have been present. Shared exposures (between OIF and GW veterans) would include war, DU, and natural environmental hazards and endemic diseases. Further details can be read in his written statement (See Appendix B – Public Comment 2).

Dettrick Stith, with SRA International, then came forward to ask why there was no grouping for black civilians in the first study presented. He noted that there were black GW veterans, white GW veterans, and white civilians included. Furthermore, he noticed that many of the disease states were higher in the black GW population than in the white GW veterans.

Dr. Golomb agreed that this is a very important question that deserves to be studied in future research. She replied that, in this case, the researchers were looking at all GW veterans with CFS as a group, and that the civilians that were in the existing CFS registry – who were people who self-selected to participate in that registry – happened to be white. Dr. Golomb stated that it didn't originally occur to the researchers that there would be significant racial differences, so they didn't plan for that. The disparities were only noticed in the process of undertaking their analysis. Thus she encouraged additional investigational studies into these racial disparities. Mr. Stith noticed that PTSD was quite a bit higher in black GW veterans than in their white counterparts. Dr. Golomb acknowledged the importance of this condition.

Maj. Nichols then came forward to back up what Mr. Bunker said about the need for standards to be set regarding the GW population. She also called for comparison of normal cancer rates in the civilian population by age and sex to be a standard research procedure in these studies. She then thanked the Committee for all their work, and asked if it would be possible for any information be disseminated (i.e. in hard copy) to some of the veterans prior to the presentations (e.g. findings of the neurocognitive studies discussed the previous day would have been helpful to have seen before launching into the PowerPoint).

Carol Hamilton, a member of the audience from the ALS therapy development institute, then came forward to thank the Committee and the researchers. She also wanted to remind the Committee (and put a hope out) that they (the Committee, associated researchers and her organization) have a concurrent research investigation for therapeutic research development.

Chairman Binns then called for any remaining members of the public to come forward with questions or comments.

Robert Walsh, from the NGWRC, said that he has been heavily involved working on an leishmaniasis case involving in utero transmission with Janice Brown's family (Ms. Brown was a woman who, before she passed away and before the Committee existed, was involved in GW issues related to leishmaniasis, for which she was criticized). In reviewing some of her work after the case got thrown out of district court, the NGWRC ran through the WHO list, which listed nearly every GW illness/idiopathic problem for visceral leishmaniasis (an asymptomatic illness with very subtle fevers, headaches, FM-like pain, GI disturbances ultimately leading to death prior to diagnosis). Mr. Walsh encouraged the Committee to look further into this disease, and to keep up the good work.

### **Federal Advisory Committee ethics training**

Mr. Jonathan Gurland  
Office of General Counsel

At this point, Mr. Jonathan Gurland, with Staff Group 3 of the General Counselor's Office, came forward to provide a brief, educational ethics training to the Committee members. Specifically, Mr. Gurland went through the document received by all Committee members who were special government employees, in order to outline the relevant rules of ethics for everyone.

During the training, Dr. Meggs asked a hypothetical question regarding an instance as follows: Someone shows up at his clinic, and as a physician he sees the patient. If it turns out that this patient was exposed to water at Camp Lejeune that had been contaminated by solvents, would Dr. Meggs be able to offer an opinion as a physician seeing a patient without transgressing ethical boundaries.

Mr. Gurland replied that if the issue (of whether there was a cause and effect between the water and Camp Lejeune and the medical condition) was not raised before the Committee, there would be no ethical concern at all.

Chairman Binns thanked Mr. Gurland and then called on Lord Morris to share any words he might have.

### **Final Comments**

Lord Morris began by introducing his colleague, Sue Freeth, from the Royal British Legion, which is the definitive voice of the ex-service community in Britain. He felt that the proceedings of the past few days had been hugely successful, as far as he and his British colleagues were concerned. U.S. and British troops fought side-by-side in the war to liberate Kuwait, so he feels that it is entirely appropriate for representatives of their respective countries – Parliamentary and Scientific alike – to be working in the closest possible rapport to address the problems and needs of those who came back from the Gulf in broken health, and the dependents of those who have died since the conflict. "Of

all the duties it falls to Parliamentarians to discharge, none is more compelling as a priority than to act justly to citizens who are prepared to lay down their lives for their country, and the dependents of those who did so. There was no delay in the response of our troops to the call of duty in 1990 and 1991, nor should there have been delay in discharging in full our debt of honor to them. That was, and remains, the best way – better by far than words of praise – of showing our regard for the men and women from our two countries who fought so gallantly in the Gulf War.” Lord Morris has been a member of the Parliament at Westminster for the last 44 years. His interest in this policy area is informed also by long ministerial experience in the U.K., and no less importantly, he stated, by his work here in Washington since 2002 with the Congressional Committee of Inquiry into GW illnesses. Congressional leaders extended him the honor, uniquely – he thinks – for a non-American, to join Christopher Shays and his colleagues on equal terms on the days of the meetings of Congressional inquiry. That experience made it crystal clear to Lord Morris that he had much to learn from their [the U.S.] example in prioritizing the legitimate claims of veterans – more particularly, in this case, Gulf War veterans, many of whom still have medically unexplained illnesses. Lord Morris then said that, though it might not be entirely up to date, his understanding was that federal expenditure has exceeded \$408 million on research on GW illness. The figure in Britain is \$17 million, since 1991. Lord Morris stated that that itself spoke to the hugely important work that Chairman Binns and the Committee has been doing. Lord Morris then expressed his admiration for the rest of the Committee, including Jack Melling (representative member from the U.K.) and expressed excitement over the upcoming release of the report.

Chairman Binns thanked everyone from the United Kingdom and asked if there were any further questions or comments.

Dr. Goldberg requested that everyone who would be receiving the honorarium of payment sign and return the letter of agreement, and send receipts for travel so that they could also be reimbursed. He also requested that if anyone’s travel expenditures exceeded the federal reimbursement limits, that they notify Dr. Goldberg at the VA as soon as possible to get approval in advance.

Chairman Binns then adjourned the meeting.

# Clinical Profiles of ALS in Gulf War Veterans

Edward J. Kasarskis, M.D., Ph.D.  
Chief, Neurology Service  
VA Medical Center

Cynthia Shaw Crispin Chair for ALS Research  
Department of Neurology  
University of Kentucky  
Lexington KY

## Outline of Presentation

- What is ALS?
- How do you make a diagnosis of ALS?
- What causes ALS?
- How is ALS managed?
- ALS/Gulf War Connection

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## ALS: The Disease

- Amyotrophic Lateral Sclerosis (ALS; "Lou Gehrig's Disease")
- Human, age-associated neurodegenerative disease
  - Due to selective death of spinal and cortical motor neurons
- Prevalence: 5-8 cases/100,000
- Incidence: 1-2 cases/100,000 annually



## ALS Population Studies

- Prevalence studies
  - 55-70 years
- Incidence studies
  - Increase with each decade
  - Data get fuzzy >80 years
- Male > Female :: 3:2

## Amyotrophic Lateral Sclerosis: "Charcot's Disease"

- In Europe
  - "Motor Neuron Disease": A spectrum of disorders
    - ALS
    - PLS (Primary Lateral Sclerosis)
    - Spinal Muscular Atrophy
    - Progressive Bulbar Palsy
    - Etc.



## ALS: The Disease

- Insidious onset of weakness
  - Limb-onset
  - Bulbar-onset
- Progression and regional spread of weakness
- Little effective treatment
  - Riluzole (Rilutek®)
- Mean survival: 4-5 years
- Terminal phase
  - Limb paralysis
  - Inability to speak, swallow
  - Respiratory insufficiency
  - Preserved awareness

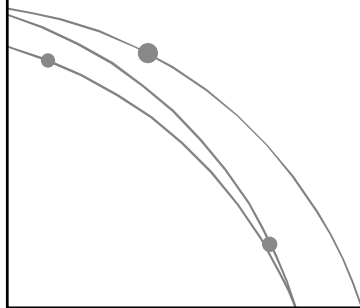
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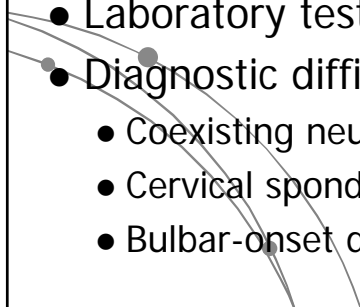
## ALS Diagnosis

- No biomarkers of the disease
- Clinical diagnosis



## ALS: Diagnostic Approach

- El Escorial research criteria (May 1990)
  - UMN and LMN signs coexisting in a region
  - Relatively preserved sensory, sphincter, ocular, cognitive, and autonomic function
- EMG evaluation
- Laboratory testing: eliminate ALS mimics
- Diagnostic difficulties
  - Coexisting neuropathies (e.g., diabetes)
  - Cervical spondylosis
  - Bulbar-onset disease





## ALS: Diagnostic Approach

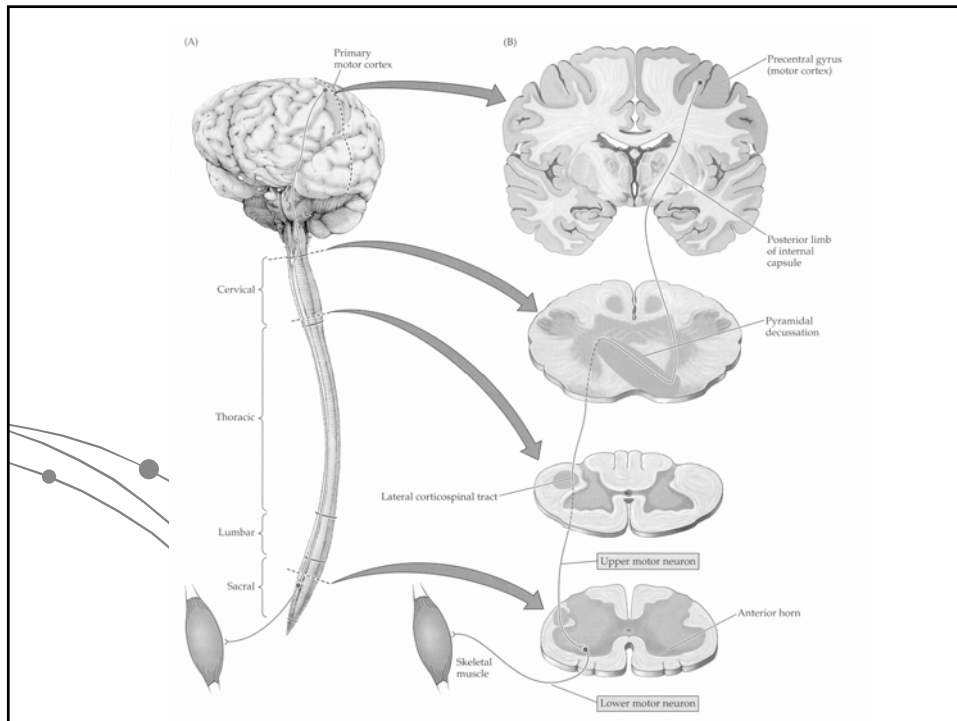
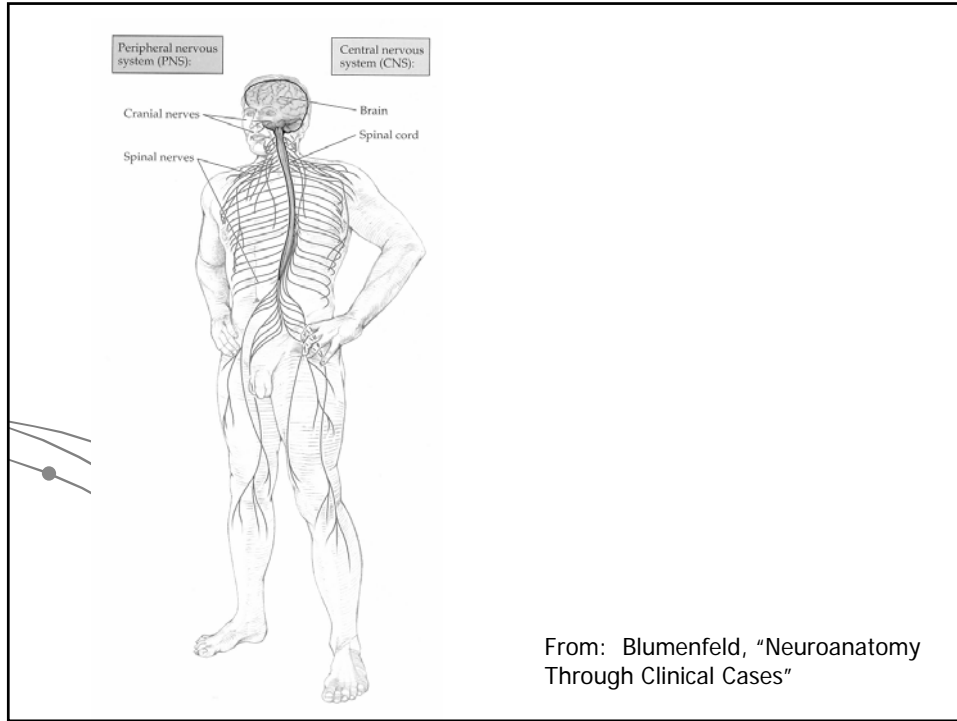
- El Escorial research criteria (May 1990)
  - UMN and LMN signs coexisting in a region
    - LMN signs
      - Muscle atrophy
      - Fasciculation
      - Weakness
    - UMN signs
      - "Weakness"
      - Spasticity
      - Pathological reflexes
  - Relatively preserved sensory, sphincter, ocular, cognitive, and autonomic function
    - Fronto-temporal dysexecutive syndromes: impaired planning and judgment, impulsive behaviors, pseudobulbar laughing and crying

## ALS: Diagnostic Approach

- EMG evaluation
- Laboratory testing: eliminate ALS mimics
  - Thyroid
  - Vitamin B12
  - HTLV-1 antibodies
  - Heavy metal screen
  - Immunofixation electrophoresis
  - Search for immune antibodies (Sensory motor neuropathy panel)
  - Genotyping
- MRI imaging of neuraxis
- Muscle and nerve biopsy
- Diagnostic difficulties
  - Coexisting neuropathies (e.g., diabetes)
  - Cervical spondylosis
  - Bulbar-onset disease

## Outline of Presentation

- What is ALS?
- How do you make a diagnosis of ALS?
- What causes ALS?
- How is ALS managed?
- ALS/Gulf War Connection



## The Concept of Motor Neurons and the Motor Unit

**Diseases of Motor-Sensory Unit: Regional Classification**

- Motor neuron**
  - Primary motor neuron diseases
  - Progressive muscular atrophy
  - Primary bulbar palsy
  - Amyotrophic lateral sclerosis
  - Werdnig-Hoffmann disease
  - Poliomyelitis
  - Tetanus
- Dorsal root ganglion**
  - Herpes zoster
  - Friedreich's ataxia
  - Hereditary sensory neuropathy
- Spinal nerve (dorsal and ventral roots)**
  - Disc extrusion or herniation
  - Tumor
- Plexus**
  - Tumor
  - Trauma
  - Idiopathic plexopathy
  - Diabetic plexopathy
- Peripheral nerve**
  - Metabolic, toxic, nutritional, idiopathic neuropathies
  - Arteritis
  - Hereditary neuropathies
  - Infectious, postinfectious, inflammatory neuropathies (Guillain-Barré syndrome)
  - Entrapment and compression syndromes
  - Trauma
- Neuromuscular junction**
  - Myasthenia gravis
  - Lambert-Eaton syndrome
  - Botulism
- Muscle**
  - Duchenne's muscular dystrophy
  - Myotonic dystrophy
  - Limb-girdle muscular dystrophy
  - Congenital myopathies
  - Polymyositis/dermatomyositis
  - Potassium-related myopathies
  - Endocrine dysfunction myopathies
  - Enzymatic myopathies
  - Rhabdomyolysis

Spinal cord lesion (anterior horn cells and motor nuclei of brainstem)

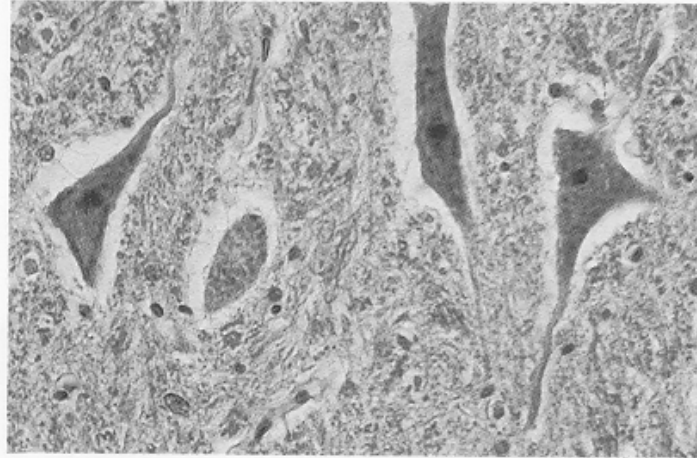
Compromised nerve supply to muscle

Muscle atrophy

REMAINING INNERVATED AND FUNCTIONING MUSCLE FIBERS

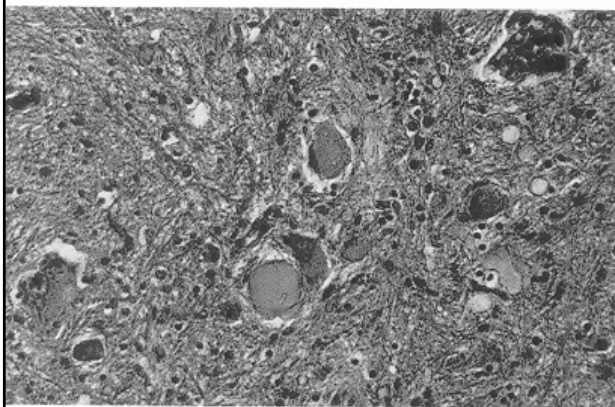
APPLIED NEUROLOGY 2005

## What do Motor Neurons Look Like?



Anterior horn of spinal cord with normal motor neurons (luxol-fast blue with H and E stain)

## Pathology: What Happens in ALS?



## History of ALS

- 1824—Charles Bell
  - Function of anterior vs posterior nerve roots
- 1850—Aran
  - “Progressive spinal muscular atrophy”
    - 1851—Duchenne studied Aran’s patients electrically
    - Became the “Aran-Duchenne Syndrome”
- 1853—Cruveilhier
  - Described the pathology of an ALS case
    - Atrophy of anterior nerve roots
- 1865—Charcot
  - Autopsy of “Primary Lateral Sclerosis”
    - Associated clinical signs of spasticity with pathology in the lateral columns of the spinal cord

## History of ALS

- 1869—Charcot and Joffroy
  - “Two cases of progressive spinal muscular atrophy with lesions of the gray matter and anterolateral fascicles of the spinal cord”
- 1874—Charcot
  - First used the term, “Amyotrophic Lateral Sclerosis”
  - Also used the term, “Primary sclerosis of the lateral columns without muscular atrophy” (PLS)
  - Returned to Aran’s original patient material
    - Some re-defined as “Charcot-Marie-Tooth”
- 1933—Brain
  - First coined the term, “Motor Neuron Disease”

## Theories of Motor Neuron Degeneration/Death

- Oxidative stress
- Glutamate excitotoxicity
  - Glial cell dysfunction
- Lack of trophic support for motor neurons
  - Axonal transport
- Exogeneous environmental toxins
  
- Not transmissible/infectious
- Not a deficiency disorder

## ALS Epidemiology: Identifying Risk Factors for ALS

- Age
  - Age <40 years
    - Incidence ~0.1/100,000
  - Age >65 years
    - Incidence ~2/100,000
- Gender
  - M:F :: 1.2-4:1
- Positive Family History
  - SOD1 mutations, alsin
- "Clusters"
  - Western Pacific (Guam) ALS/PD
- Military Service



## ALS Epidemiology: Identifying Risk Factors for ALS

- Possible Risk Factors for ALS
  - Neurotoxicant Exposures
    - Pb, Hg
    - Pesticide (insecticides, herbicides)
    - Volatile solvents
  - Occupations
    - Electrical workers
    - Farmers
  - Trauma
    - Skeletal trauma, fractures
    - Severe electrical shock with unconsciousness
  - Vigorous physical activity
    - Heavy manual labor
    - Athleticism

## Epidemiology: Identifying Risk Factors for ALS

- Lifestyle Factors
  - Cigarette smoking
  - EtOH
  - BMI
- Diet
  - High fat intake
  - High glutamate intake
  - Low fiber, antioxidant intake
- Other Factors Not Widely Investigated
  - Infectious agents
  - Co-morbidities, OTC drugs
  - Residential factors
    - Home pesticide exposure
    - Residential proximity to industry

## Established Risk Factors: Age & Sex

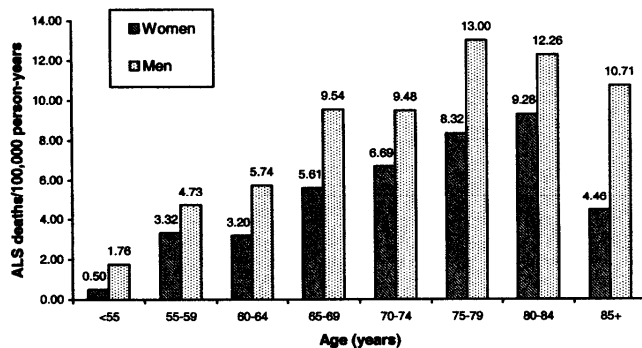


FIGURE 1. Amyotrophic lateral sclerosis (ALS) death rates in US men and women from the American Cancer Society's Cancer Prevention Study II cohort, 1989–1998.

## Established Risk Factors: Genetics

- Sporadic ALS (SALS)
  - ✓ 90% of all ALS cases
- Familial ALS (FALS)
  - ✓ 10% of all ALS cases
  - Median age of onset 35
  - Mostly autosomal dominant
  - 25% associated with a defect in the gene encoding Cu, Zn, Superoxide dismutase (SOD1)
    - Over 100 mutations defined at the SOD1 locus
    - A4V is most common SOD1 mutation in North America

## Epidemiological Risk Factors for ALS

- More or less established
  - Age
  - Male gender
  - Caucasian race?
  - Genetic
    - Sporadic vs Familial
      - CuZn Superoxide Dismutase (CuZnSOD, SOD1)

## Other Putative Risk Factors

- Occupation/environment
  - Rural residence
  - Military
- *Possible* environmental risk factors:
  - Professional sports: football, soccer
    - mechanical trauma
  - heavy physical labor
  - electrical injury/EMF exposure
  - pesticide / herbicide exposure
  - heavy metal exposure (mercury, lead, nickel), Welding?
  - exposure to chemicals used in plastics manufacturing
  - occupation as an commercial airline pilot/navigator or electrician

## ALS: Genetic Risk Factors

### Sporadic (90%) vs Familial (10%)

- Some familial cases (~30%) linked to mutations in CuZn Superoxide Dismutase (CuZnSOD, SOD1)
  - Autosomal dominant inheritance pattern
  - A4V most common genotype in US
    - Young onset; rapid progression
- Chromosome 16 locus
- VEGF
- Dynactin
- Senataxin
- TDP43

## Current Research Directions in ALS Basic Science

- Basic Biology of the Motor Neuron
  - Oxidative stress and mitochondrial dysfunction
  - Axonal transport; Axonal cytoskeleton
  - Excitotoxicity
- New genes in Mendelian families
- Biomarkers
- Etiologies of ALS
  - ALS/PD of Guam—Cycad, BMAA
  - Military service
  - Civilian occupations
  - Gene/environment

## Outline of Presentation

- What is ALS?
- How do you make a diagnosis of ALS?
- What causes ALS?
- How is ALS managed?
- ALS/Gulf War Connection

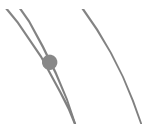
## Clinical Drug Trials in ALS: Lack of Truly Effective Therapy

- N-acetyl cysteine
- BDNF
- BCAA
- Celocoxib
- CNTF
- Creatine
- Cyclosporine
- Dextromethorphan
- Gabapentin
- GDNF
- Indinavir
- Interferon beta-1a
- IGF-1
- Lamotrigine
- Lymphoid irradiation
- Nimodipine
- ONO-2506
- Pentoxifylline
- **Riluzole**
- Selegiline
- THC-346
- Topiramate
- Verapamil
- Vitamine E
- Xaliproden
- AEOL 10150
- Arimoclomol
- Ceftriaxone
- CoQ10
- IGF-1 Polypeptide
- Minocycline
- Sodium phenyl butyrate
- Talampanel

## Current Approach to Management of ALS

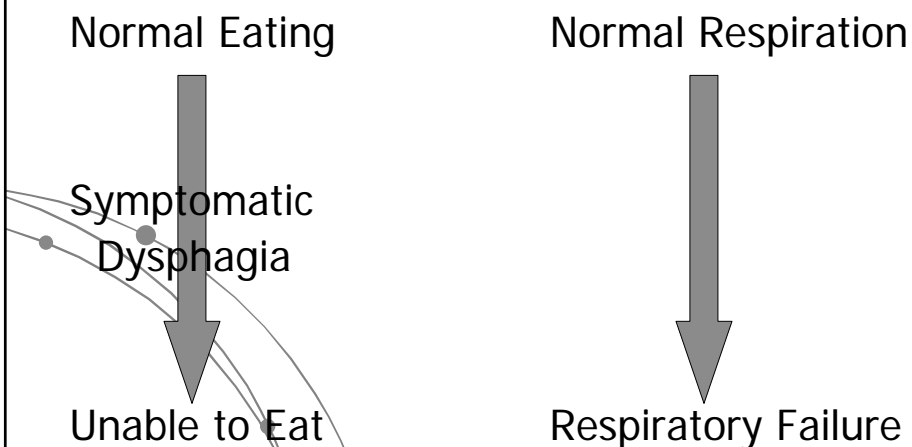
### **PRACTICE PARAMETER: THE CARE OF THE PATIENT WITH AMYOTROPHIC LATERAL SCLEROSIS (AN EVIDENCE-BASED REVIEW)**

R.G. MILLER, MD, J.A. ROSENBERG, MD, D.F. GELINAS, MD,  
H. MITSUMOTO, MD, D. NEWMAN, MD, R. SUFIT, MD, G.D. BORASIO, MD,  
W.G. BRADLEY, DM, FRCP, M.B. BROMBERG, MD, PhD, B.R. BROOKS, MD,  
E.J. KASARSKIS, MD, PhD, T.L. MUNSAT, MD, E.A. OPPENHEIMER, MD, and  
THE ALS PRACTICE PARAMETERS TASK FORCE\*



## The Realities of ALS

### Natural History



## The Realities of ALS

### Diagnosis

Normal Eating

Symptomatic

Unable to Eat

Normal Respiration

FVC = 50%

Respiratory Failure

## Current Research Directions in ALS

### Clinical Research

- Defining the clinical limits of ALS
  - Fronto-temporal "dementia"
- Earlier diagnosis
- QOL
- Clinical drug trials
  - Improving designs
  - Futility studies
  - Drug cocktails

## Outline of Presentation

- What is ALS?
- How do you make a diagnosis of ALS?
- What causes ALS?
- How is ALS managed?
- ALS/Gulf War Connection

## Military Service in the Gulf War as a Risk Factor for ALS





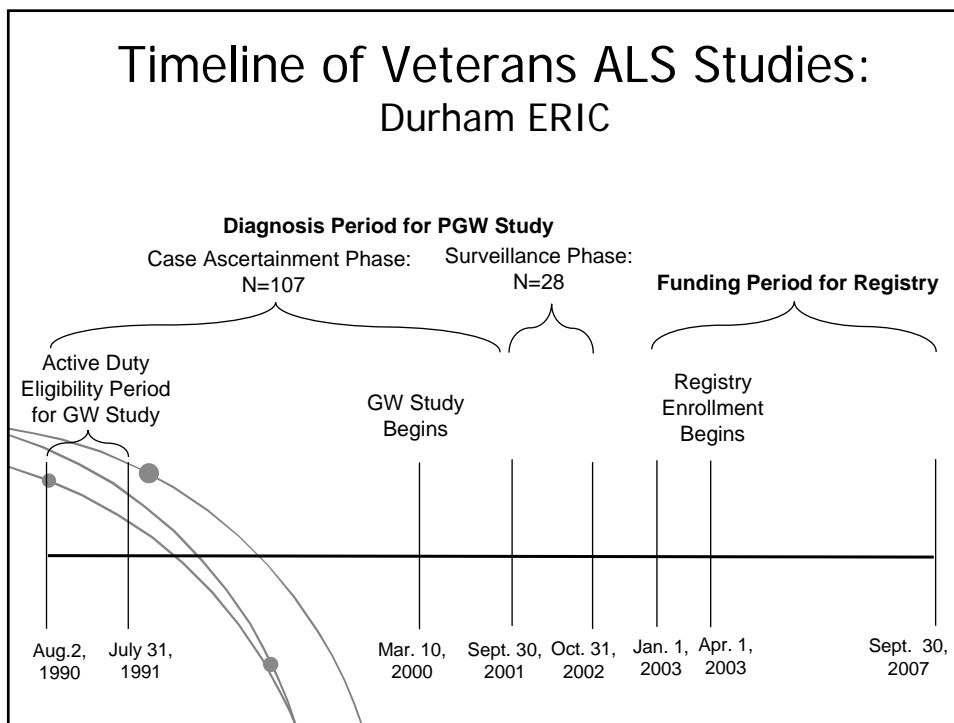
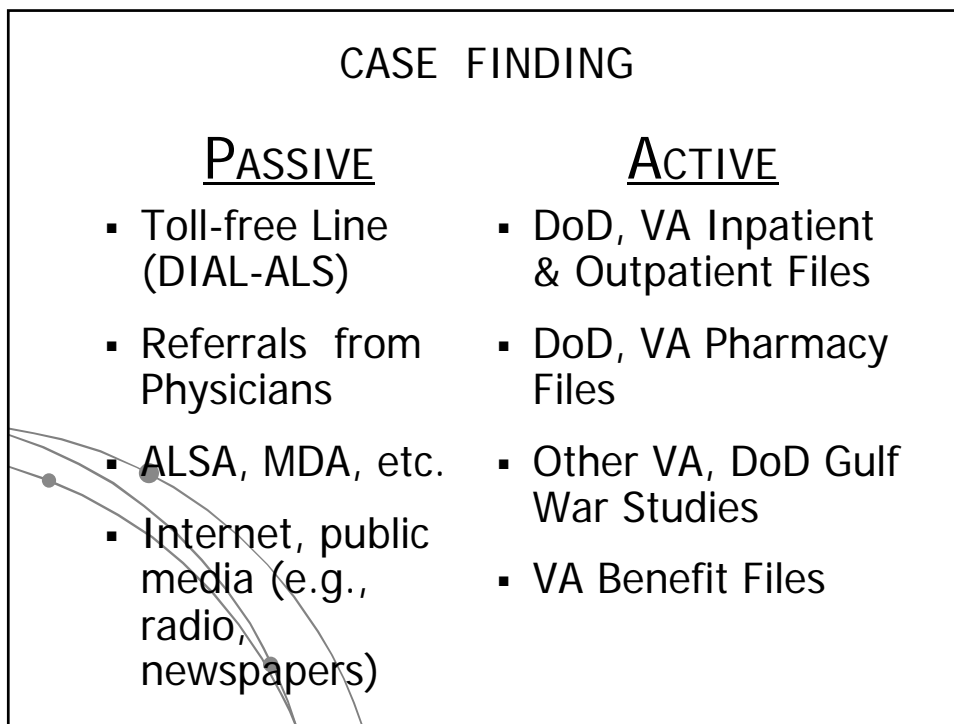
## Background: ALS in Veterans

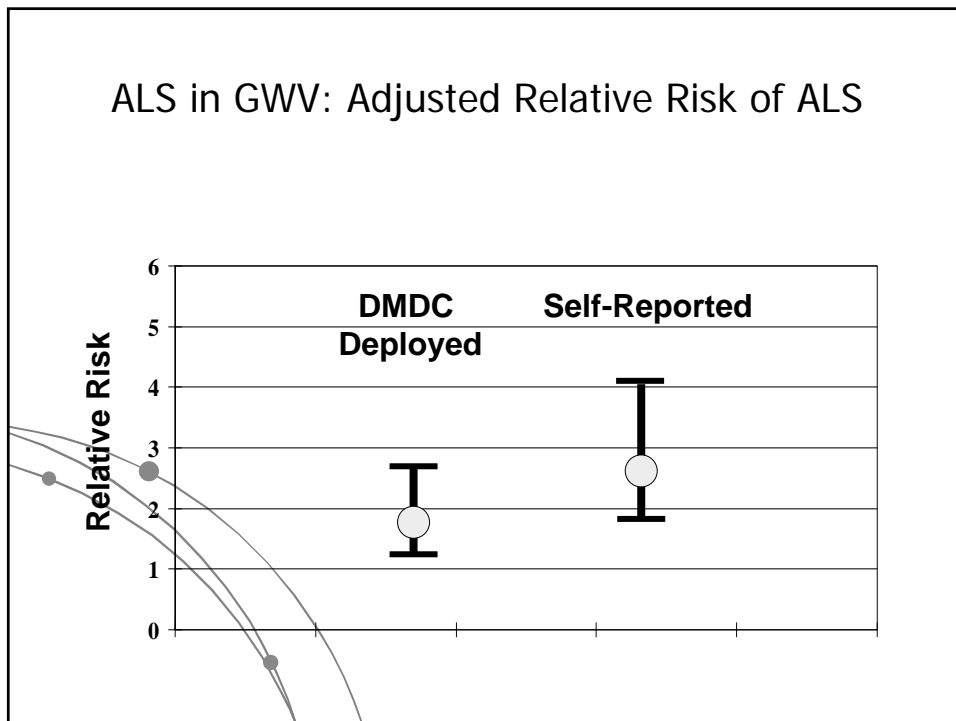
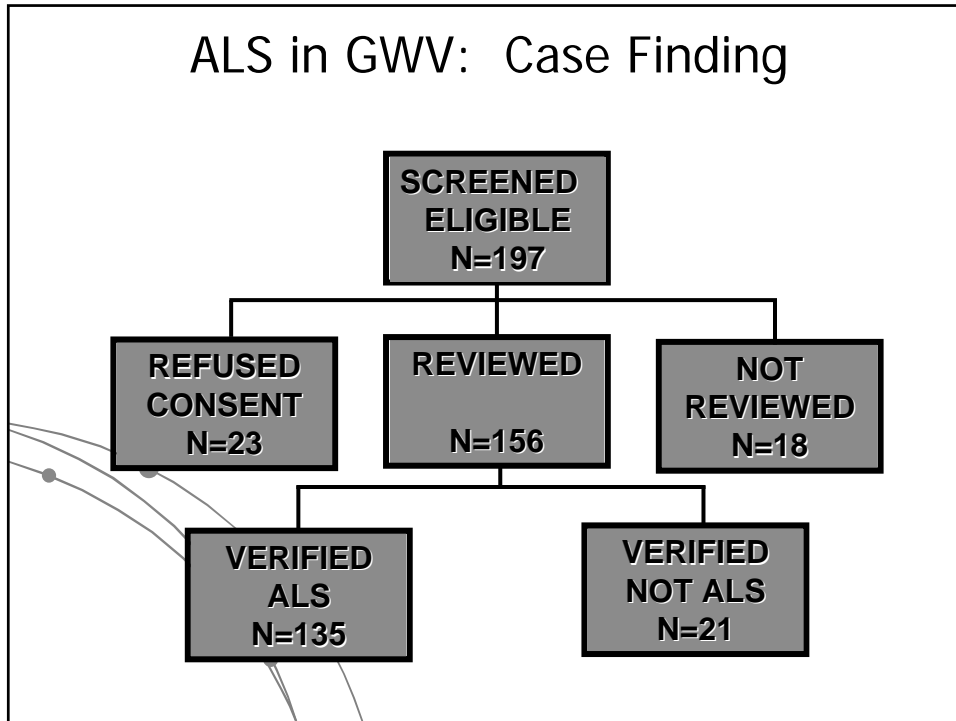
- ALS in Gulf War Veterans (VA CSP #500):
  - Case Finding: 107 cases in 2.5 million Active Duty
  - Increased risk of ALS in veterans deployed to the Persian Gulf (1990-1991) compared to active duty, non-deployed veterans (RR=1.92, 95%CL = 1.29, 2.84)
  - Significantly elevated risks for deployed Air Force and Army personnel

*Horner et al., Neurology (2003)*

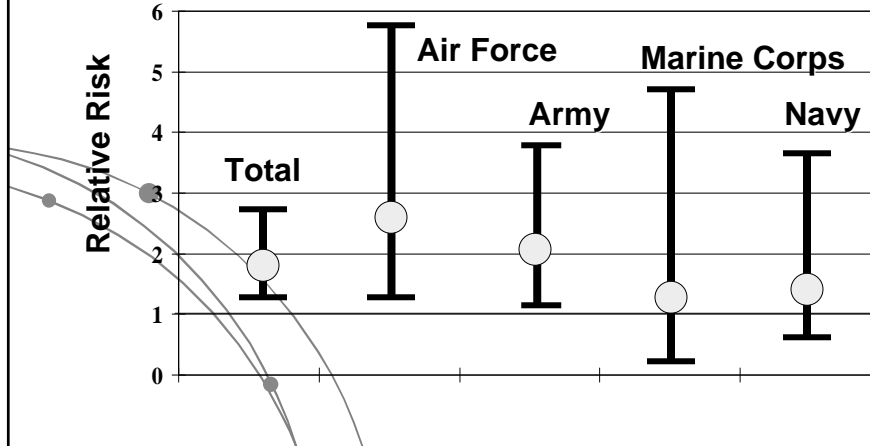
## STUDY POPULATION

- All Military Personnel on Active Duty Between 8/2/90 and 7/31/91
- Target Population: Those who were Deployed to S.W. Asia
- Primary Referent: Those who were not Deployed to S.W. Asia





### ALS in GWV: Branch-Specific Adjusted Relative Risks of ALS DMDC Deployment



### Goals of Current Study

- Define the clinical characteristics of deployed and non-deployed veterans with ALS from the Persian Gulf War
- Evaluate the hypothesis that there may have been a "Persian Gulf Variant" of ALS

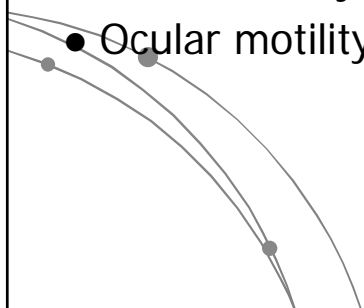
## Methodological Details of Study

- Study population: ALS subjects identified during original case ascertainment phase + surveillance phase
- Excluded cases with onset before August 1990
- Independent review of medical records by 2 ALS neurologists
- Second review to determine survival, confirm clinical findings, and resolve ambiguities
- Timing
  - Age of onset: new progressive weakness
  - Date of diagnosis: concurring 2<sup>nd</sup> opinion
  - Survival: Natural death or continuous 24 hour assisted ventilation for 2 consecutive weeks

	DMDC-Based Deployment Status (N)		Self-Reported Deployment Status (N)	
	Deployed (43)	Non-Deployed (66)	Deployed (55)	Non-Deployed (53)
Age at Onset of ALS (mean±SD)	40.1 ± 10.7	41.2 ± 8.7	40.7 ± 11.0	40.6 ± 7.9
Significance	p = 0.59 <sup>c</sup>		p = 0.95 <sup>a</sup>	
<b>Racial/Ethnic Category</b>				
White	37 (86.0%)	53 (80.3%)	47 (85.4%) <sup>a</sup>	42 (79.2%)
Black	6 (14.0%)	11 (16.7%)	7 (12.7%)	10 (18.9%)
Other	0 (0.0%)	2 (3.0%)	1 (1.8%)	1 (1.9%)
Hispanic	3 (7.0%)	1 (1.5%)	4 (7.3%)	0 (0.0%)
Significance <sup>b</sup>	p = 0.44 <sup>l</sup>		p = 0.40 <sup>l</sup>	
<b>Site of Onset</b>				
Bulbar	5 (11.6%)	15 (22.7%)	6 (10.9%) <sup>c</sup>	13 (24.5%)
Limb	37 (86.1%)	47 (71.2%)	47 (85.4%)	37 (69.8%)
Generalized	1 (2.3%)	4 (6.1%)	2 (3.6%)	3 (5.7%)
Significance <sup>d</sup>	p = 0.14		p = 0.06	
<b>24 Hour Assisted Ventilation</b>				
	14 (32.6%)	15 (22.7%)	16 (29.1%)	13 (24.5%)
Significance	0.26 <sup>l</sup>		0.59 <sup>l</sup>	

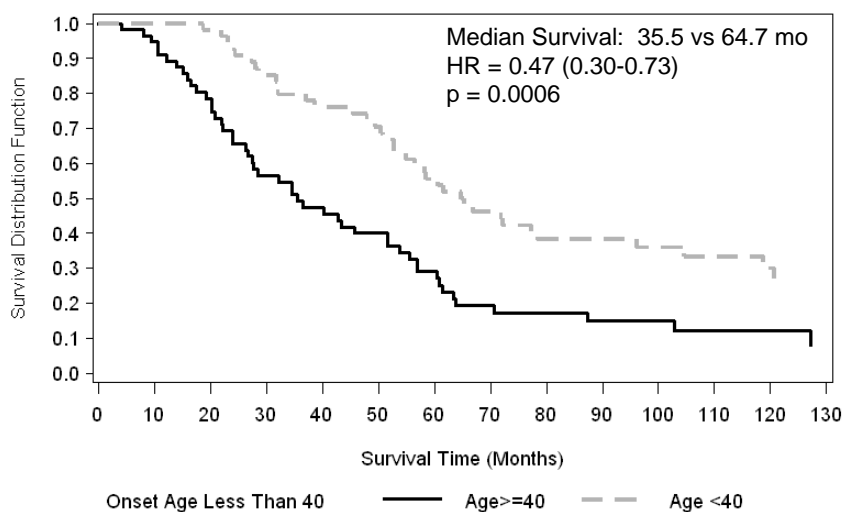
## Atypical Clinical Features

- Dementia (n=1, 0.9%)
- Sensory deficits (n=2, 1.8%)
- Extrapyraxidal signs (n=1)
- Autonomic dysfunction (n=0)
- Ocular motility abnormalities (n=0)

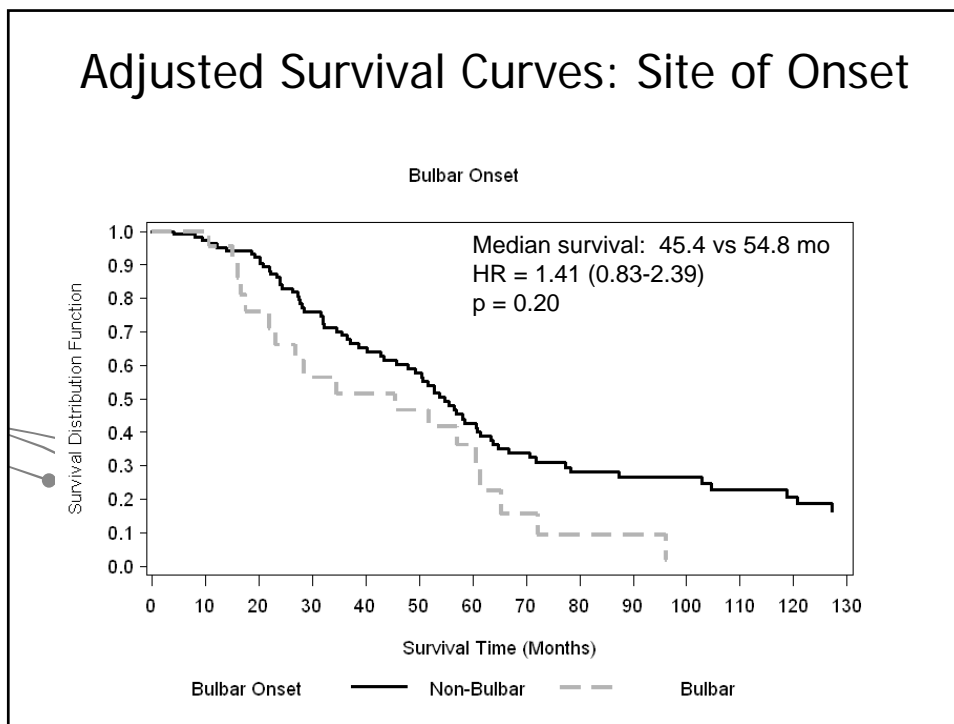


## Adjusted Survival Curve: Age at Onset

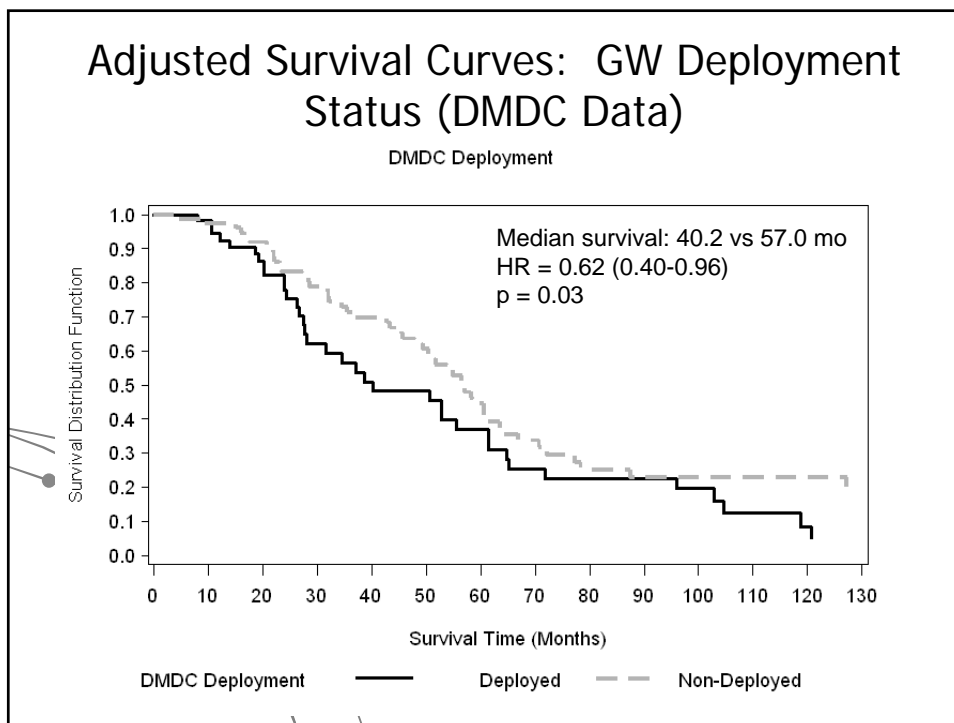
Onset Age Less Than 40

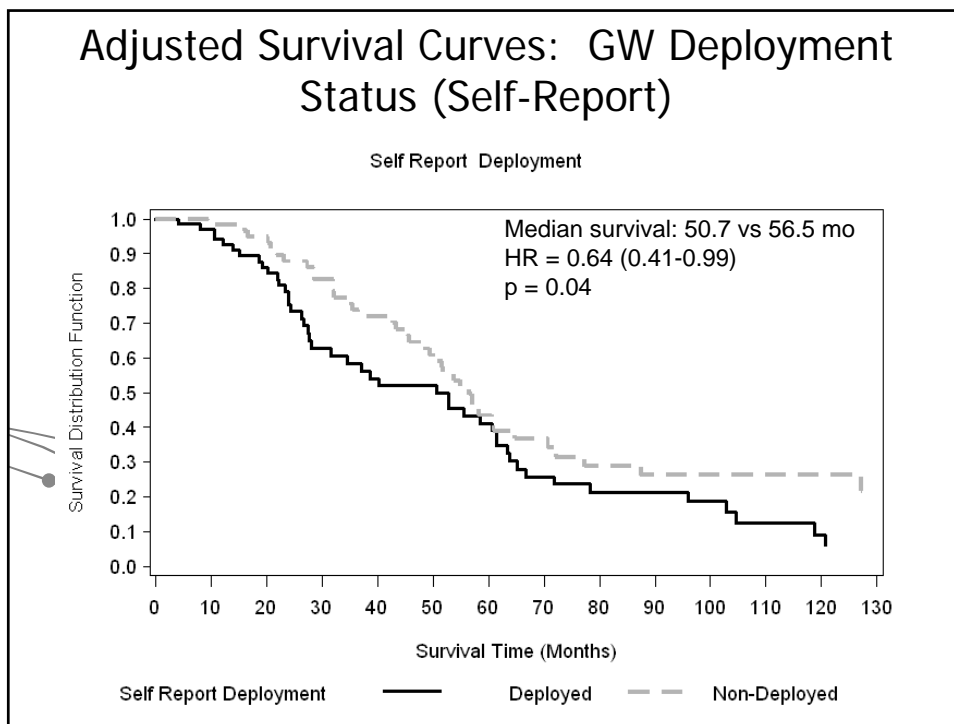


## Adjusted Survival Curves: Site of Onset



## Adjusted Survival Curves: GW Deployment Status (DMDC Data)





## Conclusions

- Confirmed the effect of age on survival
- No significant difference in Bulbar vs Non-bulbar onset in this young cohort
- High usage of 24 hour ventilatory support
- ALS in Blacks less prevalent than Whites
- ALS in Gulf War Deployed Veterans
  - No atypical clinical features
    - FTD not systematically assessed
  - Bulbar onset presentation less common (NS)
  - Survival shorter than in non-deployed veterans



## Speculations Regarding GW Survival Effect

- Source of health care
  - PCP
  - General neurologist
  - ALS specialty center (Chio et al, 2006)
- Emotional factors (McDonald et al., 1997)
- Genetic and exposure factors
  - Identical phenotype
  - Shortened survival
- Others?

## GW ALS Study Team

- E. J. Kasarskis
- J. H. Lindquist
- C. J. Coffman
- S. C. Grambow
- J. R. Feussner
- K. D. Allen
- E. Z. Oddone
- K. A. Kamins
- R. D. Horner
- ALS Gulf War Clinical Review Team
  - H. Mitsumoto
  - R. Pascuzzi
  - Y. Harati
  - R. Tim
  - E. J. Kasarskis
- M. Lyon
- D. Howard
- D. Barrett
- M. Dove
- M.A.K. Ryan
- P. Spencer
- V. Palmer
- T. Elza Mims
- L. Dempsey-Hall
- H. Rowe
- Supported by VA Cooperative Studies Program #500



## *Update on the Investigation into the ALS Outbreak among 1991 Gulf War Veterans*

*Ronnie D. Horner, PhD*

*Department of Public Health Sciences  
University of Cincinnati Academic  
Health Center*



## *Financial Support and Contributors*

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- HSR&D Program, Durham VA Medical Center
  - Drs. Allen, Coffman, Grambow and Oddone, and Ms. Linquist;
  - Dr. Miranda and her research staff
- Lexington VA Medical Center
  - Dr. Edward Kasarskis
- National Institutes of Health and University of Cincinnati
  - Drs. Ronnie D. Horner and Jun Ying

## *I. A Brief History of the Investigation*

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### *Impetus and Immediate Impact*

- Study originated in the Spring of 1999 in response to Gulf War veterans' concerns about an outbreak of ALS among their comrades
- Initial study completed in September, 2001
- December, 2001, based on the findings, the Secretary for Veterans Affairs announces ALS is now a service-connected condition for Gulf War veterans



## ***Current State of Knowledge About the Outbreak***

### **■ Is the Outbreak Real?**

- Occurrence of amyotrophic lateral sclerosis among Gulf War veterans. *Neurology* 2003; 61(6): 742-749.
- Estimating the occurrence of amyotrophic lateral sclerosis among Gulf War (1990-1) veterans using capture-recapture methods: An assessment of case ascertainment bias. *Neuroepidemiology* 2005; 24: 141-150.

### **■ Is the Outbreak Over?**

- ALS among 1991 Gulf War veterans: Evidence for a time limited outbreak. *Neuroepidemiology* 2008; 31: 28-32.

## ***Lingering Issues About the Outbreak***

### **■ What is the Etiology of the Outbreak?**

- GIS Analysis of the Etiology of Amyotrophic Lateral Sclerosis among 1991 Gulf War Veterans. *Neurotoxicology* (Epub).
- Clinical Characteristics of Military Veterans with ALS Who Served During the Persian Gulf War Era (1990-91). *ALS* (In press).

### **■ Is the Outbreak a Signal of a Broader Risk Associated with Military Service?**

- Prospective Study of military service and mortality from ALS. *Neurology* 2005; 64: 32-37.

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## *Presentation Objectives*

- **Review Findings on the Occurrence of ALS among Gulf War Veterans**
- **Present Findings on the Epidemic Curve**
- **Update on Analyses regarding the Etiology of the Outbreak**

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## *II. Review of Original and Updated Results: Is the Outbreak Real?*

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## *Synopsis of Study Methodology*

- **Examined Time Period of 1990-2000**
  - 1-yr Surveillance Study Added Cases Through 2001
  
- **Key Methodological Elements**
  - Population-based study: 1990-91 Active Duty Military
  - Active and Passive Case Identification
  - Medical Record Validation/Death Certificates
  
- **Annual Age-adjusted Rates and Risk Ratios**
  - Standardized to Total Military Population on Active Duty During 1991 Gulf War



## *Rate and Risk Ratio for ALS among 1991 Gulf War Military Personnel (Original)*

Population	Rate (95% CL) of ALS:		Risk Ratio (95% CL)
	Deployed	Non-deployed	
Total	0.67 (0.46, 0.88)	0.35 (0.27, 0.44)	1.92 (1.29, 2.84)
Air Force	1.21 (0.42, 2.01)	0.45 (0.27, 0.63)	2.68 (1.24, 5.78)
Army	0.66 (0.37, 0.94)	0.32 (0.18, 0.46)	2.04 (1.10, 3.77)
Marine Corps	0.33 (0.00, 0.71)	0.29 (0.03, 0.55)	1.13 (0.27, 4.79)
Navy	0.53 (0.13, 0.92)	0.35 (0.19, 0.52)	1.48 (0.62, 3.57)

Horner et al. *Neurology* 2003; 61: 742-749

***Rate and Risk Ratio for ALS among 1991 Gulf War Military Personnel (Updated)***

Population	Rate (95% CL) of ALS:		Risk Ratio (95% CL)
	Deployed	Non-deployed	
Total	0.85 (0.61, 1.08)	0.45 (0.35, 0.54)	1.90 (1.34, 2.69)
Air Force	1.32 (0.50, 2.15)	0.55 (0.35, 0.74)	2.43 (1.18, 5.00)
Army	0.88 (0.55, 1.21)	0.40 (0.24, 0.56)	2.21 (1.29, 3.80)
Marine Corps	0.33 (0.00, 0.71)	0.29 (0.03, 0.55)	1.13 (0.27, 4.79)
Navy	0.66 (0.23, .10)	0.49 (0.30, 0.69)	1.34 (0.62, 2.89)

Unpublished data

***Risk Ratio for ALS among 1991 Gulf War Military Personnel: Sensitivity Analysis***

Population	Risk Ratio (95% CL) of ALS:			
	All Cases	Strict Diagnosis	Onset Post-1991	Men Only
Total	1.92 (1.29, 2.84)	2.07 (1.34, 3.19)	1.84 (1.20, 2.83)	1.75 (1.17, 2.61)
Air Force	2.68 (1.24, 5.78)	3.06 (1.01, 11.27)	2.11 (0.91, 4.91)	2.60 (1.20, 5.62)
Army	2.04 (1.10, 3.77)	2.14 (1.07, 4.30)	2.69 (1.35, 5.38)	1.78 (0.95, 3.35)
Marine Corps	1.13 (0.27, 4.79)	0.90 (0.16, 4.93)	1.13 (0.27, 4.79)	1.09 (0.26, 4.59)
Navy	1.48 (0.62, 3.57)	1.92 (0.72, 5.15)	0.99 (0.33, 3.00)	1.41 (0.59, 3.40)

Horner et al. *Neurology* 2003; 61: 742-749



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### ***III. Summary of Results on the Epidemic Curve: Is the Outbreak Over?***

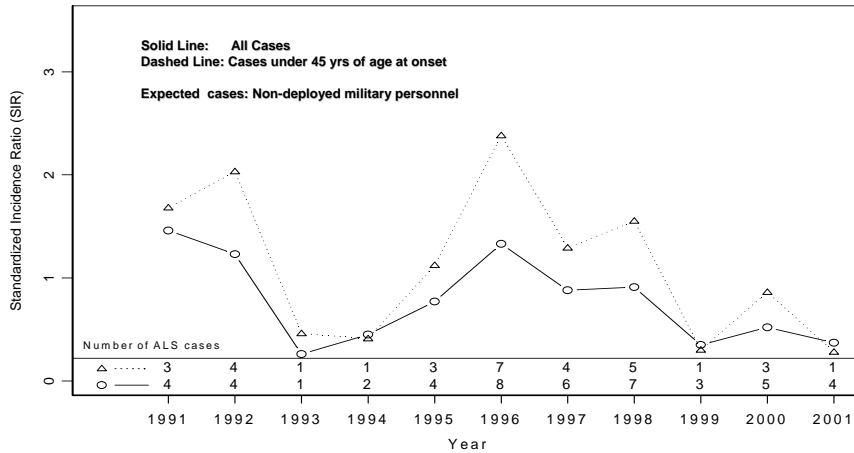
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### ***Methodology to Assess the Evolution of the Outbreak***

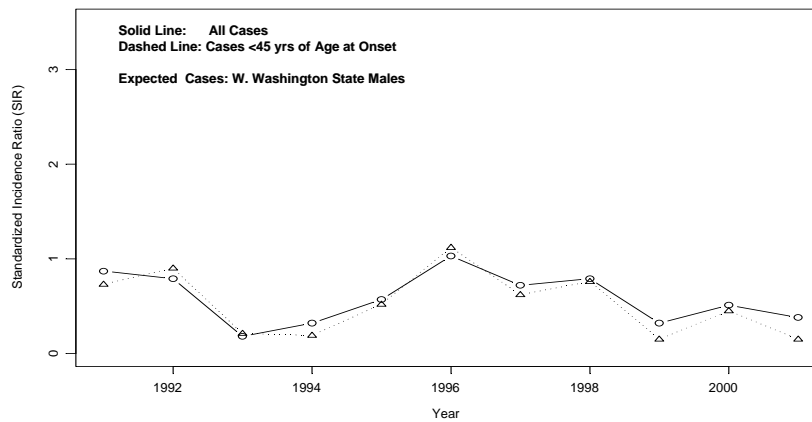
- **Examined Time Period of 1991-2001**
  - Original and 1-year Surveillance Studies
  
- **Secondary Analysis of Study Data**
  
- **Annual Standardized Incidence Ratio**
  - Expected Number of Cases Determined, Alternatively, from Gulf War-Era Non-deployed Military Population and W. Washington State Males

### *Epidemic Curve for Deployed Military Personnel (vs. Non-deployed Military)*



Horner et al. *Neuroepidemiology* 2008; 31:28-32

### *Epidemic Curve for Deployed Military Personnel (vs. General Male Population)*



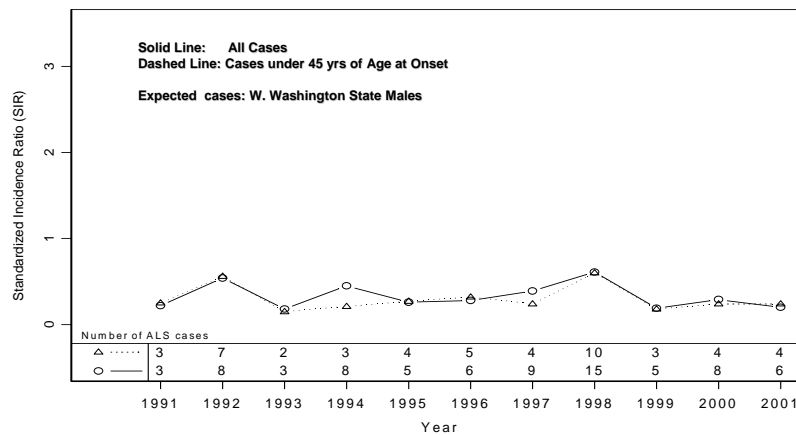
Horner et al. *Neuroepidemiology* 2008; 31: 28-32

## *Is Military Service, per se, a Risk Factor for ALS?*

- Weiskopf Study: 2-fold higher risk of ALS among those with any military service.
  - Increasing risk with increasing number of wars during military service
  
- W. Washington State Study: Additional Evidence?
  - Half of men had served in military
  - Overall Observed Rate: 2.12 per 100,000 per year
  - Anecdotal observation: 2-fold greater risk among men who had served in military but rates statistically unstable



## *“Epidemic Curve” for Non-Deployed Military Personnel (vs. General Male Population)*



Horner et al. *Neuroepidemiology* 2008; 31: 28-32

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***IV. Update on Analyses  
Relating to the Etiology of  
the Outbreak: What  
Caused the Outbreak?***

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***Current Studies Relevant to Understanding  
the Etiology***

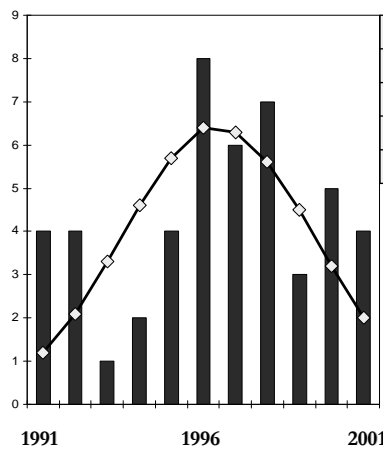
- **Sartwell's Model to Assess Likelihood of Common Source or Common Time Point of Exposure**
  - Shape of Cumulative Distribution of Case Onset
  
- **GIS Analysis of Spatial "Hot Spots" in the Theater of War (Dr. Miranda)**
  - Common Points of Exposure in Geographical Space
  
- **Persian Gulf Variant of ALS? (Dr. Kasarskis)**
  - Unusual Manifestation of Disease vis-à-vis Classic ALS



## *Assumptions of Sartwell's Model*

- **Multiplicative (growth) Process in Pathogenesis of Agent or Toxic By-products**
  - Threshold at which Symptoms Appear
  - Incubation Period = Symptom Onset – Time of Exposure
- **Inherent Individual Variation in Incubation Period**
- **Functional Form of Onset Distribution Independent of Incubation Period Length and Agent Dosage**
- **A Lognormal Distribution Infers:**
  - Common Source of Exposure
  - Common Time of Exposure

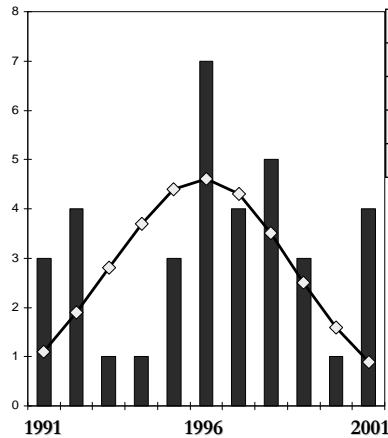
## *Distribution of Time of Onset Among All Deployed ALS Cases*



Goodness-of-Fit Tests for Lognormal Distribution				
Test	Statistic		p Value	
Kolmogorov-Smirnov	D	0.15782142	Pr > D	0.042
Cramer-von Mises	W-Sq	0.10629498	Pr > W-Sq	0.091
Anderson-Darling	A-Sq	0.67369320	Pr > A-Sq	0.075

Unpublished data

## *Distribution of Time of Onset Among Deployed ALS Cases <45 yrs at Onset*



Goodness-of-Fit Tests for Lognormal Distribution				
Test	Statistic		p Value	
Kolmogorov-Smirnov	D	0.12657200	Pr > D	0.053
Cramer-von Mises	W-Sq	0.10629859	Pr > W-Sq	0.092
Anderson-Darling	A-Sq	0.78108665	Pr > A-Sq	0.041

Unpublished data



## *Other Investigations into the Etiology*

- No Persian Gulf Variant of ALS is Apparent (Dr. Kasarskis)
- No Known Data on ALS as Endemic or Epidemic in Native Middle East Populations
- GIS Analyses are Ongoing (Dr. Miranda)
  - Common Points of Exposure in Geographical Space (*Neurotoxicology*)
  - Data Available on Two Specific Environmental Exposures



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## *V. Summary*

---

---

### *Summary of the Evidence To-date*

- **2-fold Increase in Risk of ALS among 1991 Gulf War Veterans**
- **Elevated Risk Probably Not Explained by Bias in Case Ascertainment**
- **Etiology Remains Uncertain; Exposures Immediately Prior to or During Deployment May Be Involved**
- **Role of Military Service, Per Se, as Risk Factor Remains Uncertain**

# National Registry of Veterans with ALS

VA Cooperative Study #500A

September 2008

Eugene Z. Oddone, MD, MHSc

Edward J. Kasarskis, MD, PhD

Kelli D. Allen, PhD



## Background: ALS in Veterans

- ALS in Gulf War Veterans (VA CSP #500):
  - Case Finding: 107 cases in 2.5 million Active Duty
  - Increased risk of ALS in veterans deployed to the Persian Gulf (1990-1991) compared to active duty, non-deployed veterans (RR=1.92, 95%CL = 1.29, 2.84)
  - Significantly elevated risks for deployed Air Force and Army personnel

*Horner et al., Neurology (2003)*



## PGW ALS Study

- No association with type of job
- No specific exposure or location
- Heavy metal and immunologic studies negative
- No difference in familial ALS
- Still small N

## Background: ALS in Veterans

- Other data show increased risk of ALS in Gulf War deployed veterans.

*Haley et al., Neurology (2003)*

- Recent study showed increased risk of ALS mortality among veterans compared to non-veterans (RR = 1.53, 95%CL = 1.12-2.09).

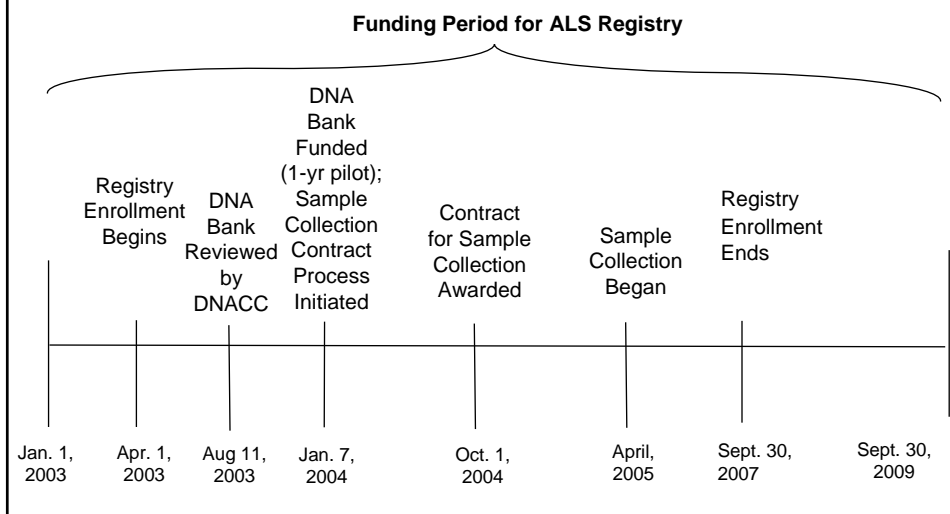
- **Secondary database study of Cancer Prevention Study II Cohort (500,000 men)**

*Weisskopf et al., Neurology (2005)*

## National Registry of Veterans with ALS: Objectives

- Identify as completely as possible all living veterans with ALS.
- Track the health status of these veterans.
- Collect important data, including DNA samples and clinical information, for studies on the causes and treatment of ALS.
- Involve veterans in other ALS-related research.

## Veterans ALS Registry Timeline



## Veterans ALS Registry Methods

- Recruitment Methods:
  - VA electronic medical records – search for ICD-9 codes in inpatient and outpatient databases
    - Identify 335.2x but prioritize those with ALS-specific code (335.20)
  - Nationwide publicity efforts: ALS Association, ALS Clinics & Centers – *important for identifying non-VA users*

## Veterans ALS Registry Methods

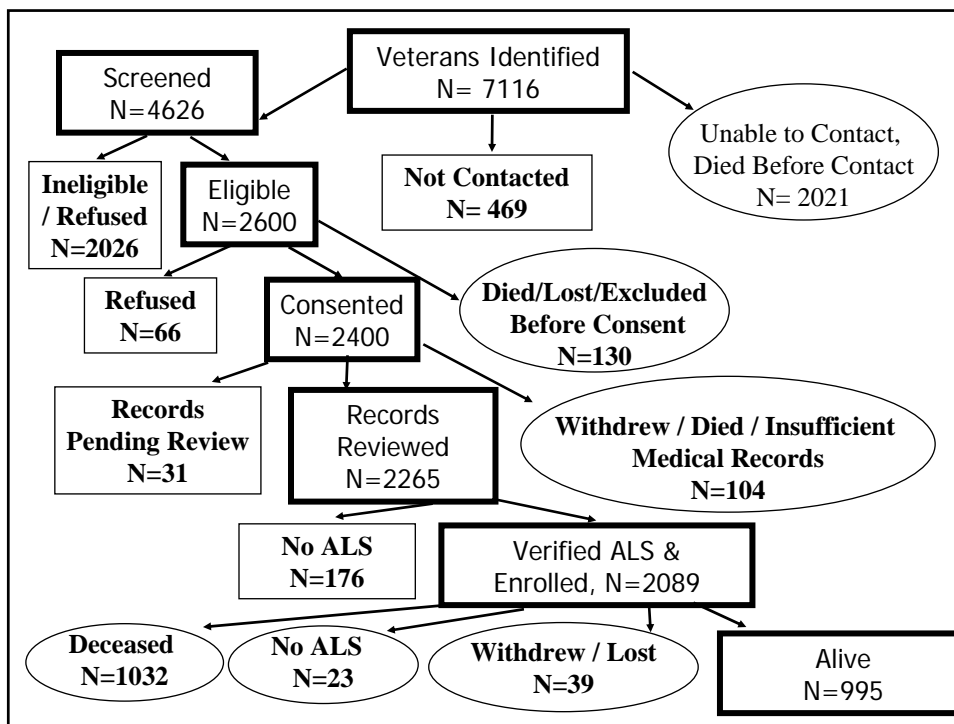
- Enrollment Procedures:
  - Telephone screener – confirm veteran status and ALS diagnosis
    - Include people with progressive muscular weakness but not definite diagnosis by MD yet
    - Collect basic demographic information, military history, date / site of symptom onset
  - Administer verbal consent

## Veterans ALS Registry Methods

- Enrollment Procedures (continued):
  - Obtain medical records (focus on neurologists)
  - Abstract relevant information
    - Date / site of onset
    - Date of diagnosis
    - EMG reports
    - UMN/LMN signs
    - Atypical features
    - Lab values
    - Family history
    - Comorbidity
    - Genetic testing
    - CT / MRI
    - Trauma history
    - Surgical history
  - Records reviewed by neurologists to confirm diagnosis (El Escorial criteria)

## Veterans ALS Registry Methods

- Follow-up telephone interviews:
  - Every 6 months
  
  - Assess functional status(ALSFRS) and treatment use (medications, CPAP, BiPAP, trach, vent)



## ALS Registry: Participant Characteristics

- Mean age = 64 years (range: 23-93 years)
- Mean age of onset: 59 years (SD = 12.2)
- 98% Male
- Race / Ethnicity:

Racial / Ethnic Group	%
American Indian	<1
Asian	<1
Black	5
White	93
Hispanic	1

*Allen et al., Neuroepidemiology (2008)*

## ALS Registry: Branch of Service

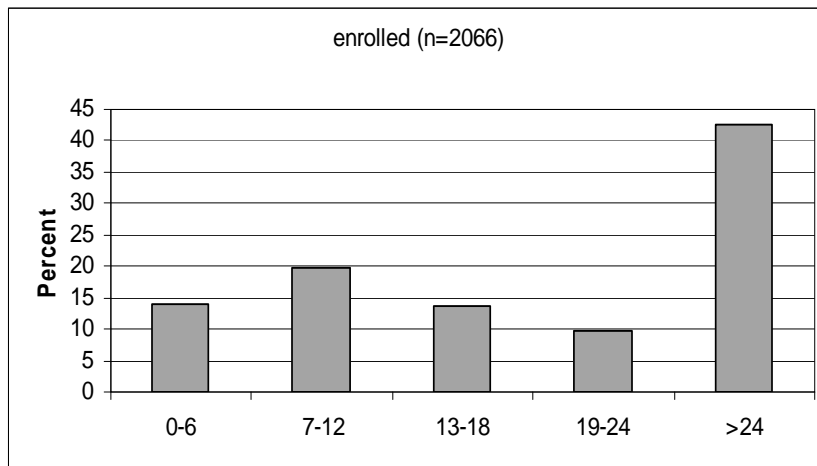
Branch	%
Army	42
Air Force	19
Navy	22
Marines	8
Reserves	4
Guard	4

## ALS Registry: Theater\*

- Any Service Outside Continental US 79%
- Afghanistan <1%
- Europe 42%
- Korea 19%
- North Africa 6%
- Pacific Islands 29%
- Persian Gulf 7%
- Vietnam 28%

\*Individual could serve in more than one theater

## Months from first diagnosis to registry enrollment



## Survival of Veterans with ALS:

(N=1085 with known death dates)

- Mean Survival Time
  - From symptom onset date to death: 4.7 years
  - From diagnosis date to death: 3.3 years
- Predictors of Survival
  - Age at Dx (per 10 yr): HR 1.41 (1.27-1.55)
  - Time to Dx (per yr): HR 0.77 (0.7-0.84)
  - Non-extremity onset: HR 1.55 (1.24-1.94)
  - Deployed to Vietnam: HR 1.73 (1.36-2.19)

*Pastula et al., ALS (2008)*

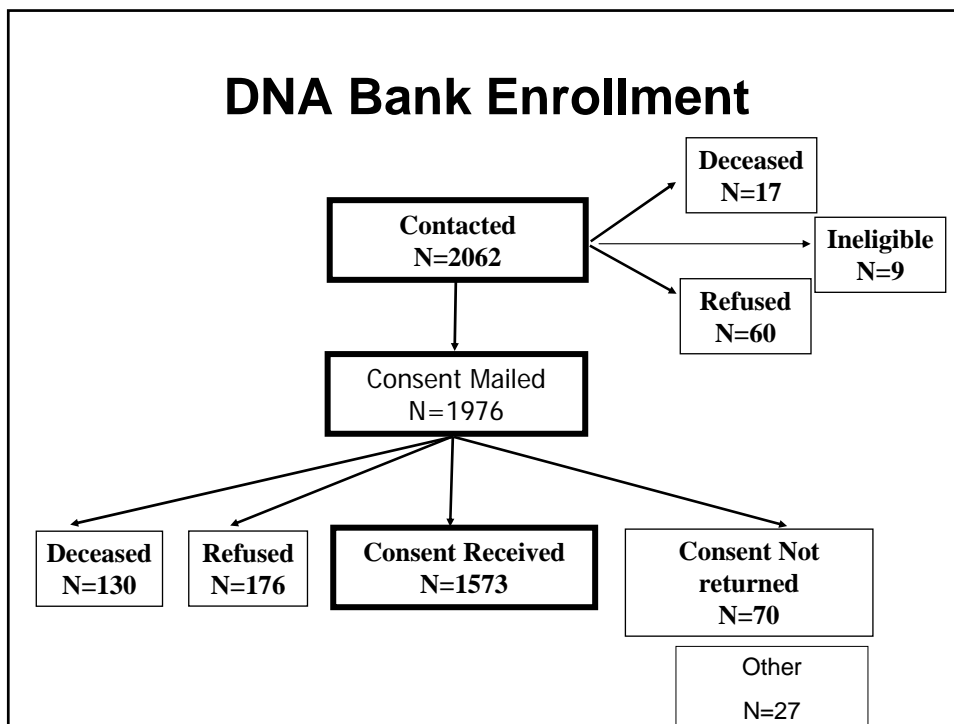
## **Veterans ALS Registry DNA Bank: Methods**

- All Registry participants asked to participate in DNA Bank, but not a requirement.
- Separate, written informed consent (via mail) required for participation.
- Participation involves agreement that DNA can be stored and used for future studies on ALS only.

## **ALS Registry DNA Bank: Methods**

- Genetic Tissue Core Laboratory (Boston VAMC)
  - Supplies kits for sample collection, sends to nurses
  - Receives completed samples from nurses
  - Extracts DNA and stores samples
  - Distributes genetic data to investigators
- DNA Coordinating Center (Palo Alto VAMC):
  - Approves all VA studies involving DNA Banking
  - Assists with protocol development
  - Monitors data collection
  - Maintains only link to participants' clinical and genetic data





## VA Investment

- ALS Registry Component
  - Approx. \$485,000/yr: 6.6 FTEE at two sites
- DNA Component
  - Approx. \$209,000/yr: 1.0 FTEE, contract for blood draw, oversight and storage
    - Blood Draw: \$188/pt
    - Ship/extract/store: \$73/pt
- Total: \$2.1 million FY 2003-2006
  - \$1,400 per enrolled pt (1,500 estimated)
    - About \$1,000 per patient to enroll in Registry and \$400 for DNA collection and storage.

## Use of Veterans ALS Registry Data

- Registry data, including DNA samples, available to VA and non-VA researchers.
- Registry Scientific Review Committee evaluates all studies requesting data use.
- VA CSP must also approve studies that request genetic data.

## Genes and Environmental Exposures in Veterans with ALS (GENEVA)

- NIEHS- and ALSA-supported case-control study with a focus on gene-environment interaction
- Subset of VA ALS registry participants enrolled as **cases** (verbal consent for interview): May 2005-present
- 10,000 potential veteran **controls** randomly selected from VBA beneficiary database: January 2006-present
  - All veterans discharged in or after 1973
  - Subset of veterans with earlier discharge year

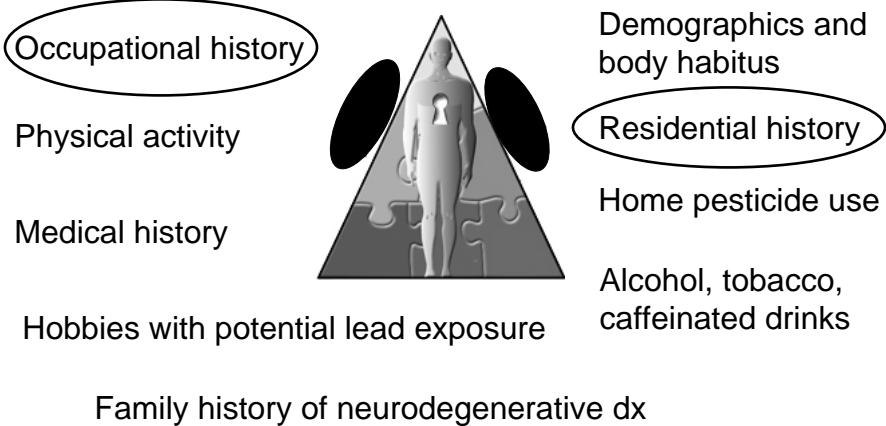
## GENEVA Study: Methods

- Cases and controls frequency-matched on age (5-year groups), sex, race/ethnicity, VA health care use
- Consenting by Durham VAMC study team, interviewing by study team and local survey research company
  - Mailed invitation letter, follow-up letters and phone calls
  - Neurological telephone screener
  - Written consent for interview and self-administered DNA collection (saliva sample)
- Structured telephone interview

*Schmidt et al., Neuroepidemiol (2008)*

## Casting a wide net...

Military history and deployment



## GENEVA Study as of 9/4/2008

	Cases	Controls
Invited to participate	1138	1739
Consented	767	568
Refusals (pre- or post-consent)	153 (18.1% of 845 alive and eligible)	1027 (60.6% of 1696 alive and eligible)
Completed	640	505

## Studies Using Registry Data

### Genetic & Biomarker

- **Biomarker Discovery of ALS among Active Duty Military**
- **Novel Cause of Motor Neuron Disease: Neuropathy Target Esterase**
- **Effect of Variation in Genes of Xenobiotic Responsive Proteins in ALS**
- **Paraoxonase (PON-1) Polymorphisms and Risk of Sporadic Amyotrophic Lateral Sclerosis (ALS) among American Veterans of Foreign Wars**
- **SELDI-MS Profiling in Veterans Deployed to the Gulf War Relative to Non-Deployed Veterans**

### Drug Trial

- **Safety and Dose Escalating Study of Oral Sodium Phenylbutyrate in Subjects with ALS**

## Studies Using Registry Data

### Specimen Collection

- **Veterans Affairs Biorepository Trust –Post Mortem Collection of Brain and Spinal Cord Tissues**

### Field Epidemiology

- **Determining the Prevalence of ALS and MS in Five Illinois Communities**

### Other

- **Emotional Disclosure in Patients with Amyotrophic Lateral Sclerosis**
- **End-of-Life Care Preferences of ALS Patients and their Physicians' Assumptions**

## ALS Study Team


- **ALS Registry**
    - Barbara Norman
    - Priscilla Webster-Williams
    - Beverly McCraw
    - Karen Juntilla
    - Lisa DiMartino
    - Laurie Marbrey
    - Cynthia Coffman
    - Jennifer Lindquist
    - Honore Rowe (Lexington VAMC)
  - **Genetic Epidemiology of ALS**
    - Silke Schmidt (PI) - Catherine Stanwyck
    - Valerie Loiacono - Kristina Nord
- Neurologists:
- Richard Bedlack (Durham)
  - Joel Morgenlander (Durham)
  - Marvin Rozear (Durham)
  - Arman Sabet (Lexington)
  - Laura Sams (Cincinnati)

# Spatial Analysis of the Etiology of ALS among 1991 Gulf War Veterans

Marie Lynn Miranda, M. Alicia Overstreet,  
Eric Tassone, Kelli D. Allen, Ronnie D. Horner




15 September 2008



## Children's Environmental Health Initiative

**A research, education, and outreach program  
committed to fostering environments where all  
children can prosper.**

**Technical expertise: spatial analysis of data**

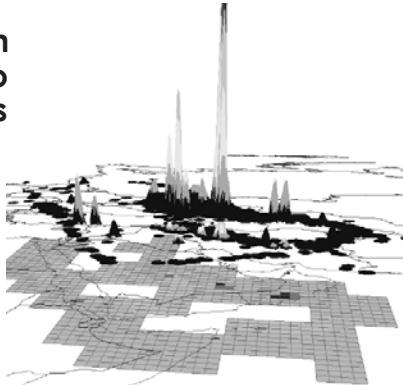


2

**Research Questions**

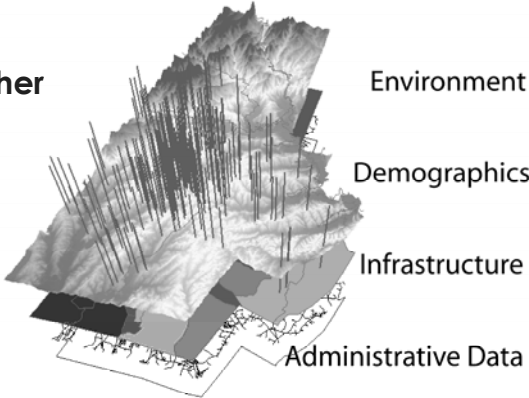
**Reports document ~twofold increase in the risk of ALS among veterans of the 1991 Gulf War over subsequent 10 years**

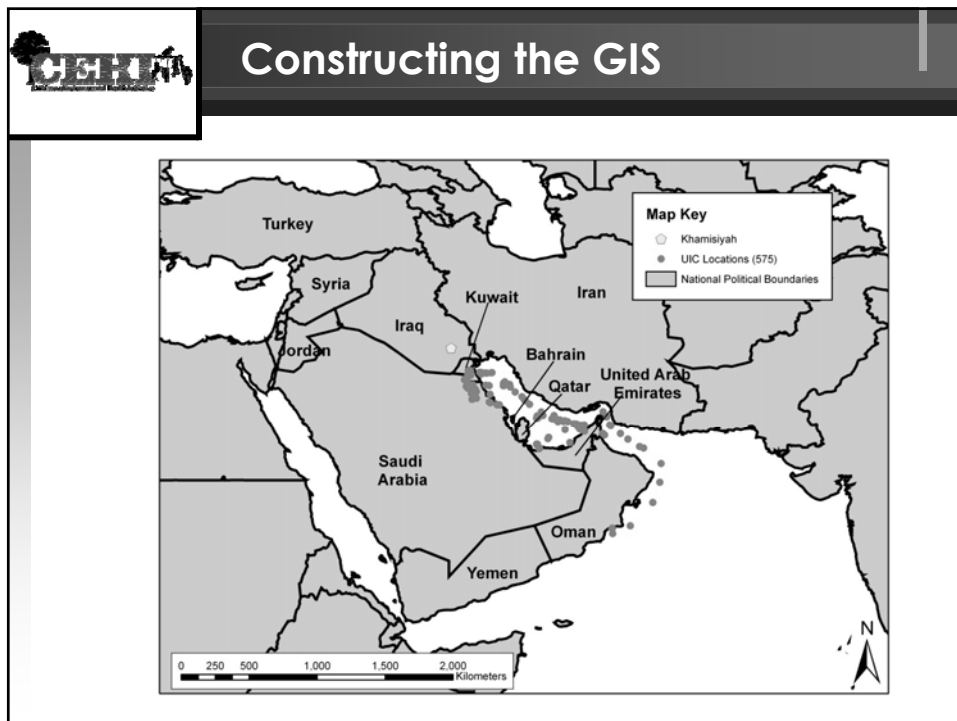
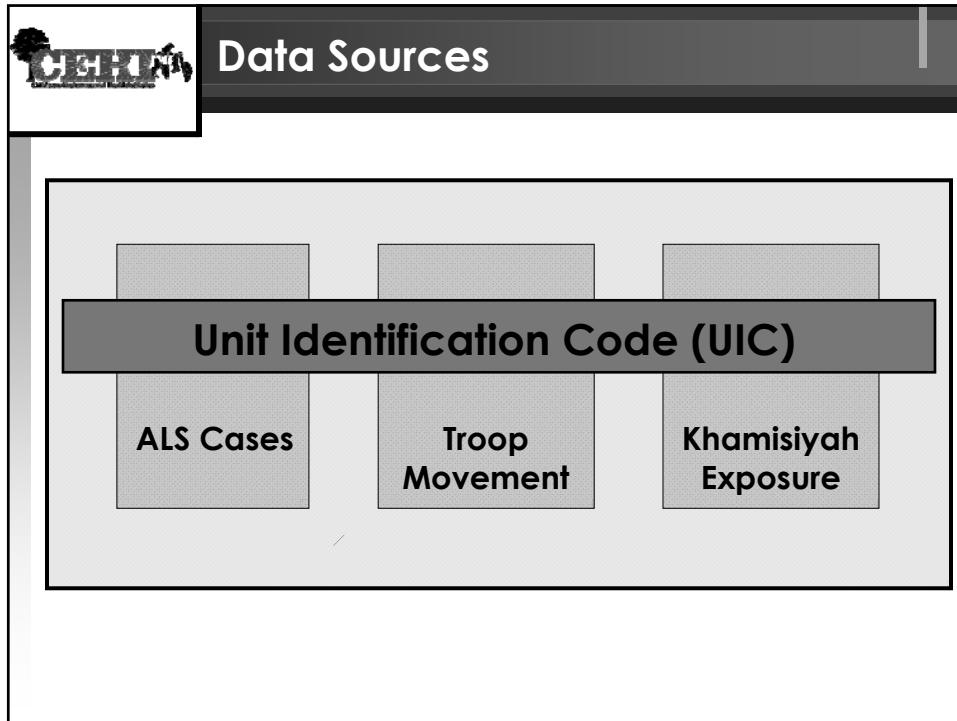
- Can a Geographic Information System (GIS) be constructed to characterize troop movements in the Gulf War theater?
- Does the GIS reveal spatial pattern in the locations of persons who eventually developed ALS?



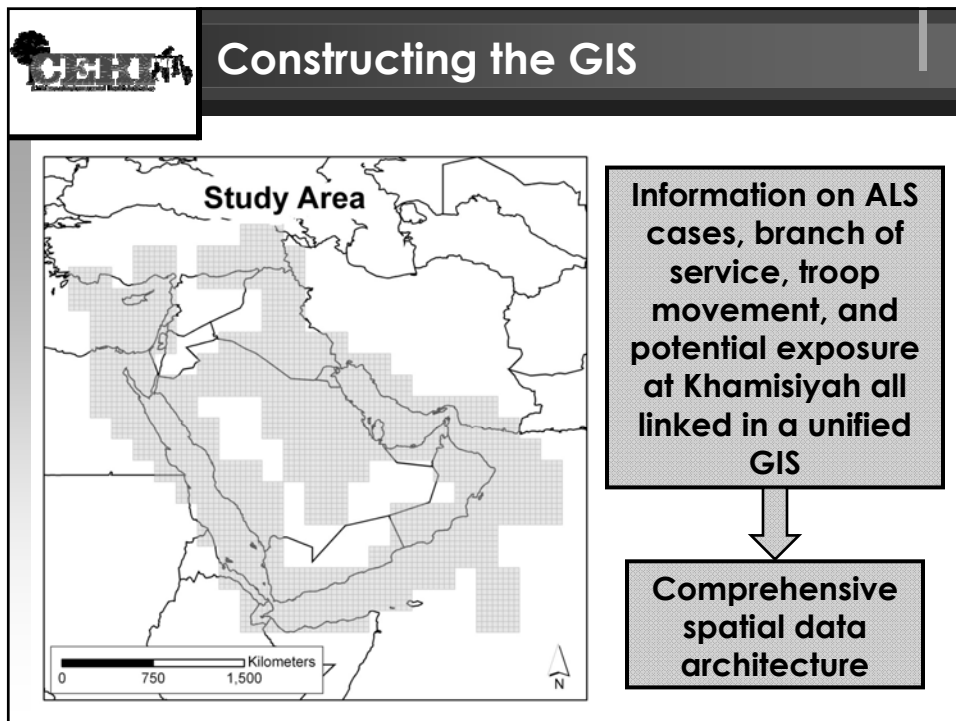
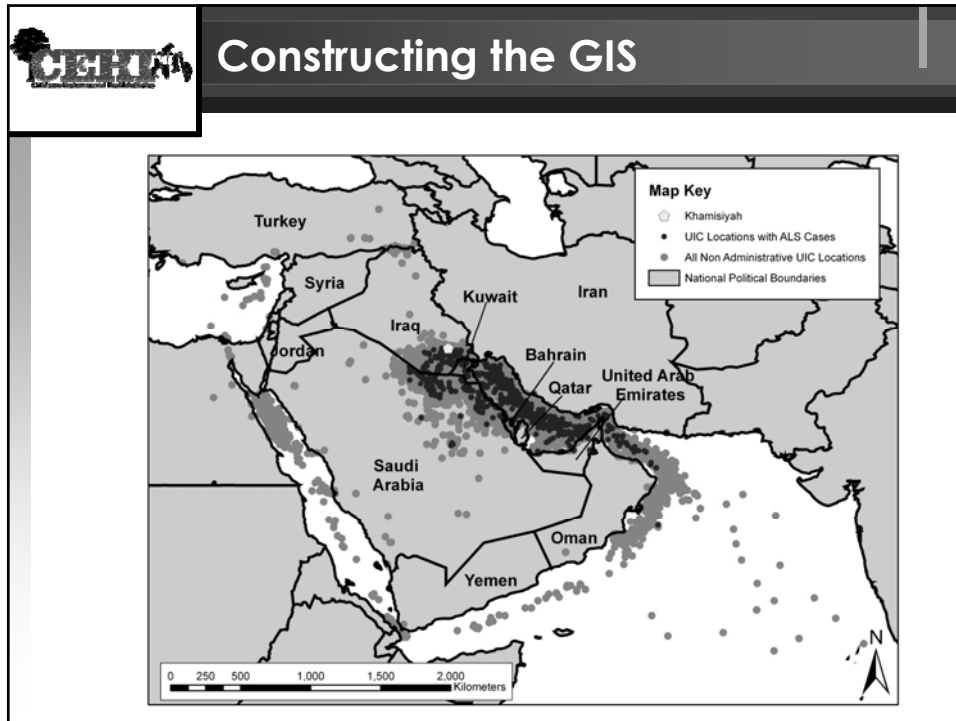
**Why Use GIS?**


- To display data geographically
- To view and analyze data in relation to other georeferenced data (integration)
- To add a spatial dimension to statistical analysis







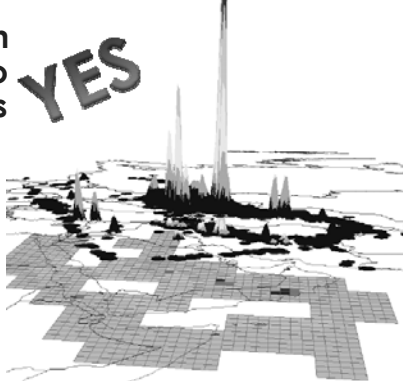



 **Research Questions**

**Reports document ~twofold increase in the risk of ALS among veterans of the 1991 Gulf War over subsequent 10 years**


- Can a Geographic Information System (GIS) be constructed to characterize troop movements in the Gulf War theater?
- Does the GIS reveal spatial pattern in the locations of persons who eventually developed ALS?

**YES**



 **Statistical Analysis**

- Bayesian Poisson regression analysis
- Four models
  1. Spatial risk only
  2. Spatial risk and branch of service
  3. Spatial risk and Khamisiyah exposure
  4. Spatial risk, branch of service, and Khamisiyah exposure
- Bayesian disease mapping techniques – specify a conditionally autoregressive (CAR) prior distribution for grid effects



## Bayesian Poisson Regression Analysis


$Y_i \sim \text{Poisson}(\mu_i)$  where  $Y_i$  is the observed disease count for  $\text{UIC}_i$  and  $\mu_i$  is the expected disease count for  $\text{UIC}_i$

**Model 1, spatial risk only:** 
$$\log(\lambda_i) = \beta_0 + \sum_{j=1}^J \beta_j \cdot x_{ij}$$

$\beta_j$  is a per-day adjustment for exposure to grid cell  $j$ , for  $j = 1, \dots, 3872$ , with corresponding covariate  $x_{ij}$  that is the number of days  $\text{UIC}_i$  was in grid cell  $j$

introduce spatial structure via a CAR prior on the  $\beta_j$ 's

$\{\beta_1, \beta_2, \dots, \beta_J\} \sim \text{CAR}(\sigma^2)$  giving  $\beta_j | \beta_{-j} \sim N(\bar{\beta}_j, \frac{\sigma^2}{\omega_j})$



## Poisson Regression Analysis

**Model 1: Spatial risk only**

$$\log(\lambda_i) = \beta_0 + \sum_{j=1}^J \beta_j \cdot x_{ij}$$

**Model 2: Spatial risk and branch of service**


$$\log(\lambda_i) = \beta_0 + \beta_{\text{Air}} \cdot I_i + \beta_{\text{Marine}} \cdot I_i + \beta_{\text{Navy}} \cdot I_i + \sum_{j=1}^J \beta_j \cdot x_{ij}$$

**Model 3: Spatial risk and Khamisiyah exposure**

$$\log(\lambda_i) = \beta_0 + \beta_{\text{Kham}} \cdot I_i + \sum_{j=1}^J \beta_j \cdot x_{ij}$$


**Model 4: Spatial risk, branch of service, and Khamisiyah exposure**

$$\log(\lambda_i) = \beta_0 + \beta_{\text{Kham}} \cdot I_i + \beta_{\text{Air}} \cdot I_i + \beta_{\text{Marine}} \cdot I_i + \beta_{\text{Navy}} \cdot I_i + \sum_{j=1}^J \beta_j \cdot x_{ij}$$



## Estimated Model Parameters

	Quantity	Estimate	95% Credible Interval
Model 2	Relative Risk, Army (referent)	1.0	N/A
	Relative Risk, Air Force	1.4	(0.6, 3.1)
	Relative Risk, Marine Corps	0.2	(0.02, 0.7)
	Relative Risk, Navy	0.3	(0.05, 0.9)
Model 3	Relative Risk, Khamisiyah	1.9	(0.9, 3.9)
Model 4	Relative Risk, Army (referent)	1.0	N/A
	Relative Risk, Air Force	1.7	(0.6, 4.1)
	Relative Risk, Marine Corps	0.2	(0.03, 0.9)
	Relative Risk, Navy	0.3	(0.06, 1.1)
	Relative Risk, Khamisiyah	1.7	(0.7, 3.7)



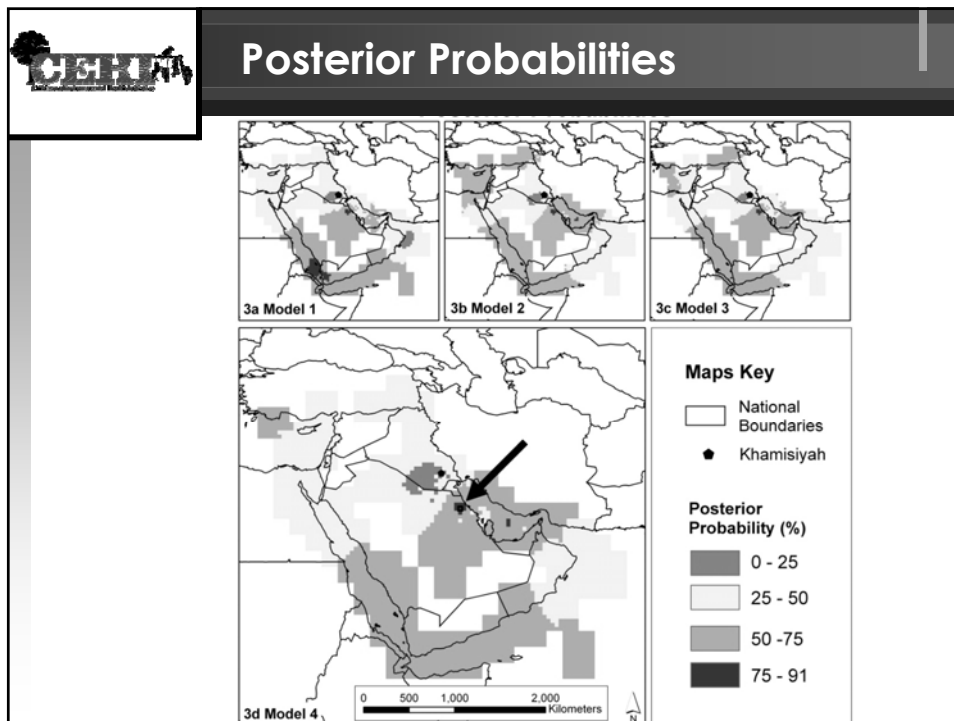
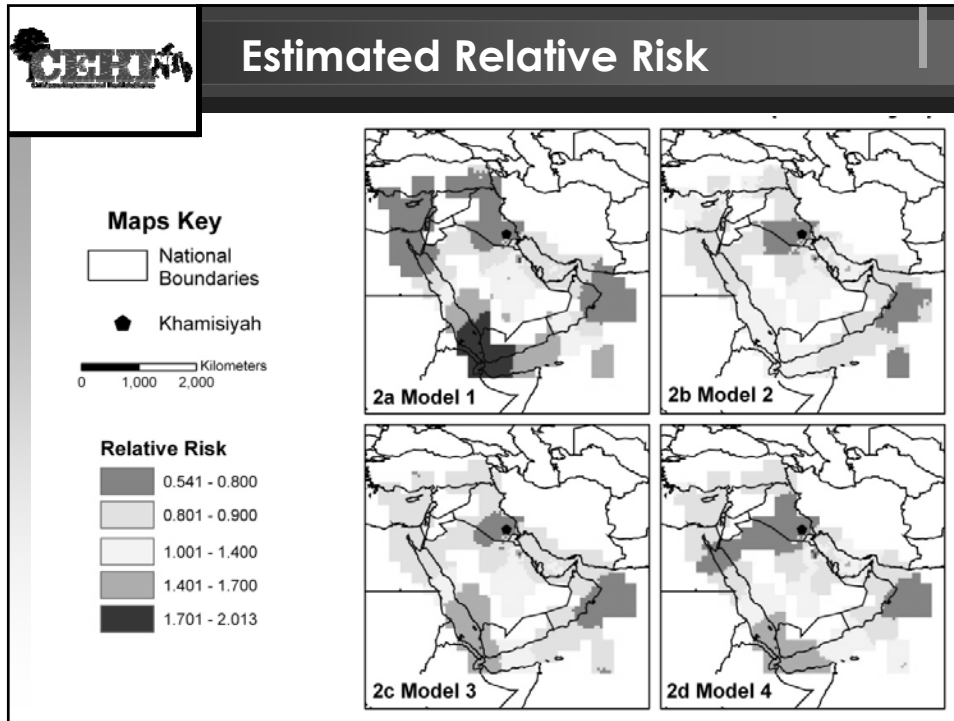
## Focusing on Model 4 Results


**Model 4: Spatial risk, branch of service, and Khamisiyah exposure**

**Estimated ALS incidence**

- 11.8/100,000 members of Air Force
- 7.1/100,000 members of Army
- 2.1/100,000 members of Navy
- 1.5/100,000 members of Marine Corps

**Estimated relative risk associated with Khamisiyah exposure = 1.7 with 95% credible interval of (0.7, 3.7) and posterior probability of elevated risk ~89%**

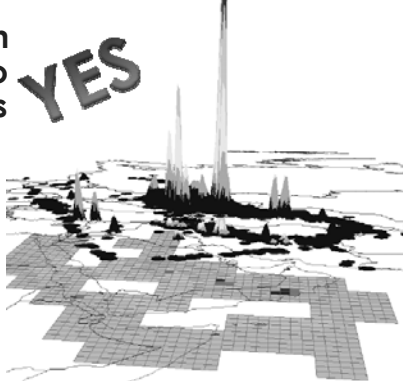



 **Research Questions**

**Reports document ~twofold increase in the risk of ALS among veterans of the 1991 Gulf War over subsequent 10 years**

- Can a Geographic Information System (GIS) be constructed to characterize troop movements in the Gulf War theater?
- Does the GIS reveal spatial pattern in the locations of persons who eventually developed ALS?

**YES**

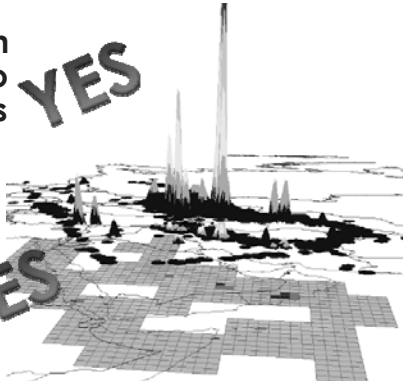



 **Research Questions**

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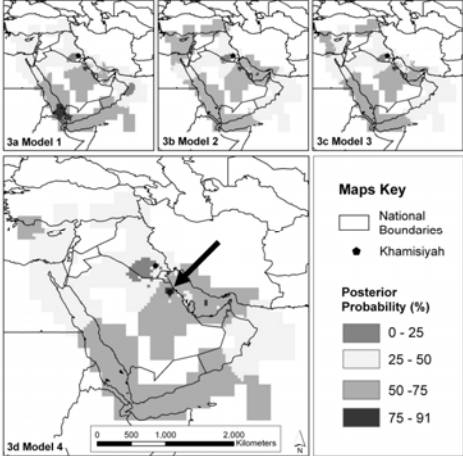
- Can a Geographic Information System (GIS) be constructed to characterize troop movements in the Gulf War theater?
- Does the GIS reveal spatial pattern in the locations of persons who eventually developed ALS?

**YES**



 **Conclusions**

- Evidence of increased risk associated with potential exposure at Khamisiyah
- Specific geographic locations of troop units are associated with an increased risk for subsequent development of ALS
- Spatial analysis can help in search for potential etiologic factors




**Maps Key**

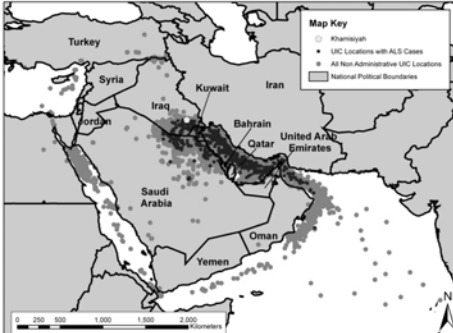
- National Boundaries
- Khamisiyah

**Posterior Probability (%)**

- 0 - 25
- 25 - 50
- 50 - 75
- 75 - 91


 **Limitations**

- Only spatial analysis
- Crude measure of potential of exposure at Khamisiyah (0/1)
- Failure to account for potential exposure from oil well fire plumes
- Problems with troop location data



**Map Key**


- Khamisiyah
- USC Locations with ALS Cases
- All Non-Administrative USC Locations
- National Political Boundaries



## Directions for Future Research

- Spatio-temporal analysis
- More detailed modeling of potential of exposure at Khamisiyah
- Inclusion of potential exposure from oil well fire plumes
- More work with USACHPPM on troop locations
- Construct spatial data architecture for troops currently deployed and undertake similar analyses

Proposal already submitted to Department of Defense



## Acknowledgements

- U.S. Army Center for Health Promotion and Preventive Medicine (USACHPPM)
- Department of Defense/Department of Veteran Affairs, CSP #500
- Office of Research Support, Duke University

<http://www.nicholas.duke.edu/cehi/>



# Is There a Deployment-Related Gulf War Syndrome?

The VA-GW Joint project

Paul H. Levine, M.D.

Sept. 17, 2008

## Three Phases

- 1) A factor analysis of a large survey conducted by Kang et al., Dept. Vet. Affairs
- 2) A clinical and epidemiologic evaluation of affected veterans and controls at the George Washington Univ. Medical Center
- 3) A laboratory approach to investigate the pathogenesis of the proposed illness

## Evidence for a Deployment Related Gulf War Syndrome by Factor Analysis

---

Department of  
Veterans Affairs-  
Environmental  
Epidemiology Service

George Washington  
University School of  
Public Health and Health  
Services

Han Kang, Dr.P.H.  
Clare Mahan, Ph.D.  
Kyung Lee, Ph.D.  
Fran Murphy, M.D.

Samuel Simmens, Ph.D.  
Heather Young, MPH  
Paul Levine, M.D.



### What is factor analysis?

---

- Statistical technique applied to a set of variables where the researcher is interested in discovering which variables in the set form coherent subsets that are relatively independent of one another
- Allows the reduction of a large number of variables into a smaller number of broad concepts (factors)

## VA-GWU Study

---

- Population based sample
- Large cohort of 15,000 Gulf War veterans and 15,000 non-Gulf War veterans
- Separate factor analysis for each group



### Distribution of Gulf War Veterans and Non-Gulf War Veterans by Gender and Unit Component

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Unit	Male	Female	Total
Active	4800	1200	6000
Reserve	4000	1000	5000
National Guard	3200	800	4000
Total	12,000	3000	15,000



## National Health Survey Population

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- Phase I-questionnaire mailed to 30,000 (15,000 deployed & 15,000 non-deployed)
- 15,817 responses from Phase I
- Phase II-telephone interviews of non-respondents
- 5,100 responses from Phase II
- 70% overall response rate



## GWU-VHA Factor Analysis Results

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- 6 factor solution produced different results for the Persian and non-Persian Gulf veterans
- 5 of the factors were of similar composition in both groups
- Persian Gulf group showed evidence of a neurological factor



## Summary of Factors

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- Fatigue/depression
- Musculoskeletal/Rheumatologic
- Gastrointestinal
- Pulmonary
- Upper respiratory
- Neurological-only in deployed group



## Neurological Factor-Deployed Only

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- Blurred vision\*
- Loss of balance/dizziness\*
- Speech difficulty\*
- Tremors/shaking\*
- Concentration/memory problems
- Irregular heartbeat
- Sudden loss of strength

\*Cluster of 4 symptoms that did not load on any of the factors in the non-deployed group



## Case Definition

---

- Reporting mild or severe problems on all of four symptoms
- 277 (2.4%) deployed met case definition
- 43 (0.45%) non-deployed met case definition although no factor was evident
- 7.8% of deployed and 1.9% of non-deployed reported at least 3 of 4 symptoms



## Epidemiologic and Neuropsychiatric Evaluation of Symptomatic Gulf War Veterans and Controls

---

Department of  
Veterans Affairs-  
Environmental  
Epidemiology Service

Han Kang, Dr.P.H.  
Clare Mahan, Ph.D.

George Washington  
University Medical Center

Samuel Simmens, Ph.D.  
Heather Young, MPH  
Paul Levine, M.D.  
Perry Richardson, M.D.  
Samuel Potolicchio, M.D.  
et al.



## METHODS

- 57 veterans in four study groups (Table 1) were evaluated by a series of examinations performed at the George Washington University Medical Center (Table 2).

## TABLE 1

### Study Groups

- **Group 1**=Deployed to the Persian Gulf with all 4 symptoms reported during or after Gulf War period. (n=27)
- **Group 2**=Not deployed to the Persian Gulf with all 4 symptoms reported. (n=11)
- **Group 3**=Deployed to the Persian Gulf with PTSD according to questionnaire checklist but none of the four symptoms. (n=15)
- **Group 4**=Deployed to the Persian Gulf and not reporting any of the 4 symptoms or PTSD. (n=4)

## TABLE 2

### Examinations performed

- Mississippi and SCID- psychiatric evaluation
- Exposure interview
- Medical and neurologic examinations
- Ophthalmologic examinations
- Electronystagmography (ENG)
- Visual evoked response (VER)
- Brain stem auditory evoked response (BAER)
- Somatosensory evoked potentials (SSEP)
- Electroencephalograms (EEG)
- Nerve conduction tests (when indicated)

## RESULTS (1)

- Study groups were generally similar although groups 1 and 2 were slightly older and the percentage of African-Americans was highest in group 1.
- Groups 1 and 2, which reported more symptoms than groups 3 and 4, appeared to have more abnormalities noted on neurological examination than groups 3 and 4.



## RESULTS (2)

- Of the 34 veterans with documented abnormalities, 23 were common neurologic problems (physiologic tremor, cervical or lumbar radiculopathy, etc.), 8 had isolated neurological abnormalities not related to clinical symptoms (isolated hyper-reflexia, isolated peripheral neuropathy, etc.) and 3 could be attributed to concurrent medical conditions.
- No significant differences between any two groups were found by visual evoked potential, brainstem auditory evoked potential response method, somatosensory evoked potentials method, or ophthalmologic tests.

## RESULTS (3)

- EEG testing showed no difference among the groups but ENG findings suggested more abnormalities in Groups 1 and 2. Review of the nine patients with reported abnormalities showed that all except two had either peripheral findings (otologic disorders) or borderline abnormalities deemed insignificant. Only three subjects (two in Group 1 and one in Group 2) had possibly significant abnormalities of central nervous system origin.
- Multiple vaccines were common but no significant inter-group differences were noted.

## RESULTS (4)

- Psychological testing indicated that 60% of study Groups 1, 2, and 3 met the clinical criteria for at least one psychiatric disorder. The diagnosis of PTSD, however, was as common in study groups 1 and 2 as in Group 3, which was selected by their meeting the criteria for PTSD on the 1995 questionnaire.

## RESULTS (5)

- Gulf-deployed symptomatic subjects were more likely to have been exposed to the Khamasiyah plume and had objective confirmation of deployment to Iraq and/or Kuwait than Gulf-deployed non=symptomatic subjects .
- There was no excess exposure, however, to total suspended particulates (TSP) .

## CONCLUSIONS (1)

- Objective neuro-ophthalmologic examination did not confirm the presence of a deployment-related neurologic syndrome.
- Interviews confirmed the severe stress, disruption, and health effects of preparation for deployment as well as deployment to the Persian Gulf.

## CONCLUSIONS (2)

- The three subjects with unexplained ENG abnormalities indicated the possible existence of a neurologic syndrome which we could not document, but the indistinguishable appearance of Groups 1 and 2 by all neurologic, ophthalmologic and psychiatric tests indicate that the putative syndrome we identified by factor analysis is not deployment-related.

## **Arylesterase activity, cytokine and cortisol levels in deployed and non-deployed Gulf war veterans with neurologic symptom complexes or PTSD**

Authors and Laboratories

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## **Laboratory Studies**

- Paraoxanase, arylesterase, butylcholinesterase and cortisol assays at the DVA Medical Center, East Orange, NJ (Dr. John Ottenweller) (A fifth group of asymptomatic civilian controls were added to this study panel)
- Cytokine assays performed at The George Washington University Medical Center Immunology Dept (Dr. Benjamin Dickens)

**Does deployment status and/or presence or absence of neurologic symptoms correlate with expression of health-related serum biomarkers in each cohort?**

Serum biomarker evaluated	Rationale
Th1-, Th2 and inflammation-associated cytokines	Immune dysregulation possible contributor to Gulf War-associated illnesses
paraoxonase/arylesterase (PON) and Butyrylcholinesterase Activity	Low activity of PON and related enzymes that hydrolyze OP may correlate with neurological disease in Gulf War-1 veterans
Cortisol	Cortisol is a stress-related hormone and could be informative

## Serum Paraoxonase (PON1) Activity

Paraoxonase was elevated in symptomatic veterans whether they were deployed or not compared to civilian controls.

Arylesterase was elevated in all veteran groups compared to civilian controls.

	Group 1	Group 2	Group 3	Group 4	Group 5
Paraoxonase (uM/ml/min)	577+81*	576+124*	479+107	518+248	245+52
Arylesterase (uM/ml/min)	111+3*	96+8*	102+7*	116+8*	65+10

\* Different from Group 5, P < 0.05

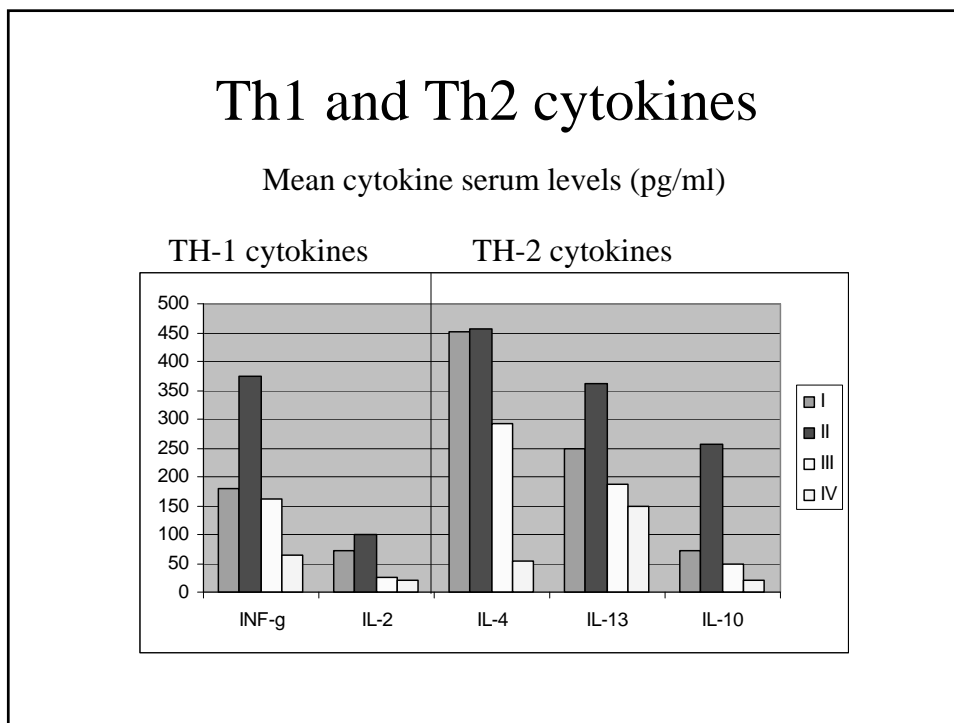
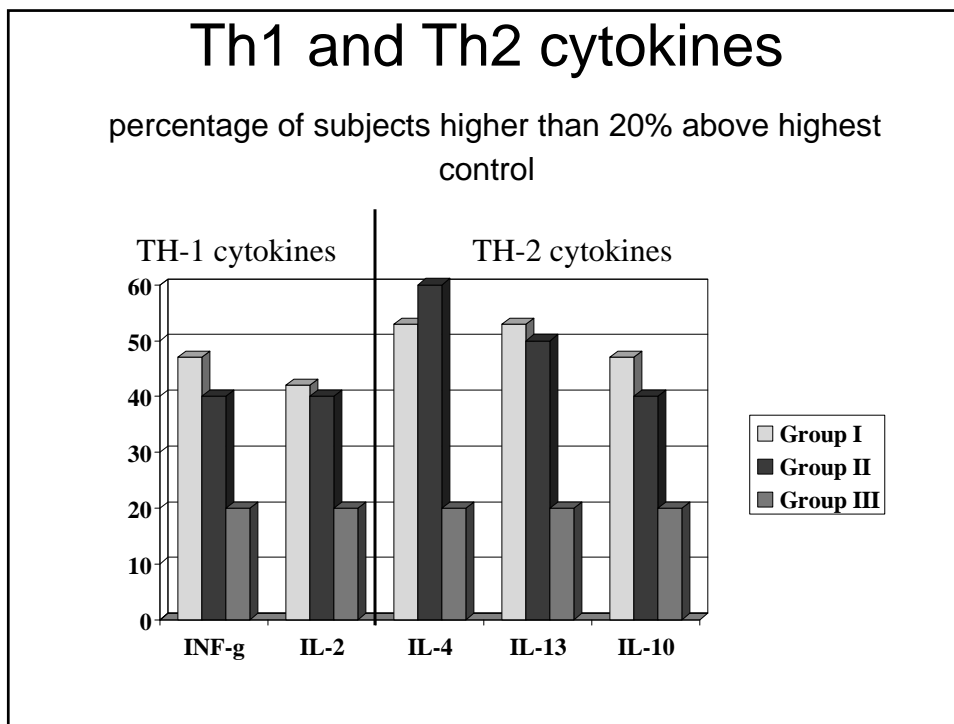
## Serum Butyrylcholinesterase Levels

- BuChE activity (uM/min/ml) and phenotype were not significantly different in the five groups.

Group 1	Group 2	Group 3	Group 4	Group 5
0.63+0.03	0.70+0.04	0.64+0.04	0.65+0.07	0.57+0.02

## Serum Cytokine Levels

- Serum levels of 10 cytokines (IL-1, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12, tumor necrosis factor- $\alpha$ , interferon- $\gamma$  and granulocyte macrophage-colony stimulating factor) were measured in Groups 1-4 using the Luminex 100 system and reagents from Upstate Biotechnologies.
- Cytokine levels were more elevated in Groups 1 and 2 than Groups 3 and 4.



## Conclusions

- 1. Paraoxanase levels were most elevated in the symptomatic veterans (deployed and non-deployed)
- 2. Arylesterase levels were increased in all groups of veterans vs. non-military controls
- 3. Cytokine levels were most elevated in the symptomatic veterans (deployed and non-deployed)
- 4. Cortisol levels did not differ among the study groups

## Overall Conclusions

- 1) The neurological symptoms reported by the veterans could be correlated with physical findings but most could be attributed to co-morbidities and not a deployment-related syndrome.
- 2) The neurological and laboratory abnormalities reported by Haley et al. could not be replicated in this cohort.



## Overall Conclusions (cont.)

- 3) The interview and cytokine data suggested a correlation between the symptoms in Groups 1 and 2 with intensive vaccination in preparation for deployment.
- 4) Prospective studies are needed to determine whether an intensive short-term vaccination program is detrimental.

## Environmental Exposures During the Gulf War (A Coalition Troop Exposure on 15 March 1991)

Rev. Dr. Joel Graves - Captain, U.S. Army, Retired

Member 1<sup>st</sup> Battalion, 67<sup>th</sup> Armored Regiment, 1<sup>st</sup> "Tiger" Brigade (Independent Task Force), a lead element in the attack into Kuwait City. After the initial attack, camped in the vicinity of Al Jahrah after Desert Storm.

## Four Goals for this Presentation

1. The Department of Defense (DOD) needs to look at this incident more closely and validate the anecdotal evidence, like they did for the Khamisiyah nerve agent exposures, so sick soldiers can be notified and receive treatment at VA hospitals, and researchers know that this is a unique exposure worth looking at and studying more closely.
2. I would like someone with the authority to ask the GAO to study this exposure incident, like the GAO did for Khamisiyah, and present the results of the plume and exposure data to the DOD and the Gulf War Research Advisory Committee.
3. VA help to increase awareness among Gulf War veterans and researchers about the Basra exposure that potentially affected many more people than Khamisiyah.
4. I would like to see the Gulf War Research Advisory Committee recommend and push for specific VX studies that look at effects and treatments, with hopefully, UTSW taking this on as well.

## Khamisiyah Review

- The Khamisiyah nerve agent exposure was a revelation to people suffering from Gulf War Illness. By accident, Army Engineers incorrectly blew up the Iraqi Khamisiyah weapons storage depot, and sarin nerve agent was released up into the air (It should have been destroyed in such a way as to minimize air exposure). The DOD and GAO did wind data studies to determine what troop units might have been exposed, and it was estimated that tens of thousands of people were potentially exposed. Given that data, the VA notified soldiers of a potential nerve agent exposure. The official disclosure of this incident gave credibility to the anecdotal stories soldier's were sharing about their exposures and health problems.
- But it didn't explain why people like me had Gulf War Illness without being in the Khamisiyah plume. All I knew was that I was exposed to something from the Basra uprising, that chemical alarms went off around us, and we all got sick - some people were very sick.

## Arms Control Today Jan/Feb 2006 Report Confirms Iraq Used Sarin in 1991

- U.S. investigators have confirmed that Iraq used chemical weapons to quash a Shiite uprising after the 1991 Persian Gulf War.
- The report marked the first outside confirmation that the regime had used chemical weapons to quell a growing 1991 insurgency.
- The report said the use of chemical weapons was an example of the "dire nature of the situation" and the regime's "faith in special weapons" that it would consider using chemical weapons *while coalition forces were still in Iraq.*



## Early Warning

By William M. Arkin

Excerpt from Washington Post Blog  
November 28, 2005

[http://blogs.washingtonpost.com/earlywarning/2005/11/another\\_saddam\\_1.html](http://blogs.washingtonpost.com/earlywarning/2005/11/another_saddam_1.html)

### William M. Arkin on National and Homeland Security

- I have a suggestion for another massacre, one that was unleashed in response to the worst instance of civil unrest since the beginning of President Saddam Hussein's rule.

What happened in this massacre bears heavily on the current health of American veterans, on our view of the competence of the U.S. intelligence community, and the current weapons of mass destruction debate.

- In a little noticed discovery, the Iraq Survey Group investigating Iraq's WMD concluded last year that the former regime dropped chemical weapons on Shi'ite rebel groups during their post-Desert Storm revolt in *March 1991*. This finding directly contradicts the Pentagon review of potential causes of Gulf War Syndrome as well as the earlier conclusions of the intelligence community which had looked into the matter.

**Toxicity of the Organophosphate Chemical Warfare Agents GA, GB, and VX: Implications for Public Protection** *Environmental Health Perspectives Volume 102, Number 1, January 1994*. This study looks at the differences between GA (tabun), GB (sarin), and VX.

1. VX does not degrade in the wind like GA and GB.
2. It gets more potent when blown.
3. The symptoms we experienced (nausea, vertigo, vomiting) are the same as with VX exposure.
4. People with more clothes on would have less exposure and therefore fewer symptoms. It also blew down on us at meal time, so it was probably ingested.

### Study Excerpts

- VX is more stable, more resistant to detoxification, less volatile, more efficient at skin penetration, and more environmentally persistent. Because of these characteristics, VX is more effective as a skin penetrant and lethal contact agent rather than as an inhalation threat. Dermal absorption is a more likely route of VX exposure than inhalation; moreover, dermal toxicity is more likely to occur from the absorption of VX aerosol or liquid than from the vapor.
- Although wind speeds of 20 mph may never be encountered in an unplanned release of VX, it is important to realize that wind speed can significantly increase the dermal toxicity of VX.
- The wide range of individual responses to dermal VX exposure, caused in part by differences in penetrability of the skin in various parts of the body, makes the prediction of a human dermal VX LD50 value difficult. Most subjects had transient symptoms of lightheadedness and some experienced nausea and vomiting; One subject became irritable, reported headache, spoke less clearly, and became confused and then irrational and agitated; and transient depressive effects on mental functioning and mood.

### Study Excerpts Continued

- The psychological effects were usually seen well before the onset of gastrointestinal symptoms in those subjects who experienced both types of effects.
- The relative potency of GA, GB, and VX varies with the route of exposure. Inhalation or percutaneous absorption of vapor or aerosol demonstrates that VX is more toxic than GB, which is more toxic than GA (i.e.,  $VX > GB > GA$ ). In comparison with GB human exposure estimates, VX is estimated to be approximately twice as toxic by inhalation, 10 times as toxic by oral administration, and approximately 170 times as toxic after skin exposure.
- VX undergoes virtually no degradation as it slowly penetrates the skin; thus, more of this compound is able to reach the bloodstream.
- *In vitro* studies suggest that VX can penetrate in unaltered form through the epidermis and dermis of the skin, penetrate through the nerve membranes, and can accumulate within the nerve cells.

## VX Characteristics

- VX is currently (as of 2008) is the most toxic nerve agent ever synthesized.[3] The median lethal dose (LD50) for humans is estimated to be about 10 milligrams through skin contact and the LCt50 for inhalation is estimated to be 30-50 mg•min/m<sup>3</sup>. [4]
- VX (O-ethyl-S-[2(diisopropylamino)ethyl] methylphosphonothiolate) is an extremely toxic substance whose sole application is as a nerve agent. As a chemical weapon, it is classified as a weapon of mass destruction by the United Nations in UN Resolution 687. Production and stockpiling of VX was outlawed by the Chemical Weapons Convention of 1993.

## VX Characteristics Cont'd

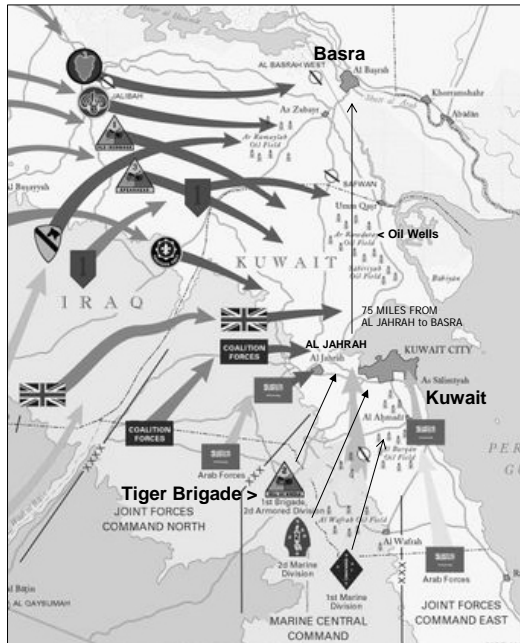
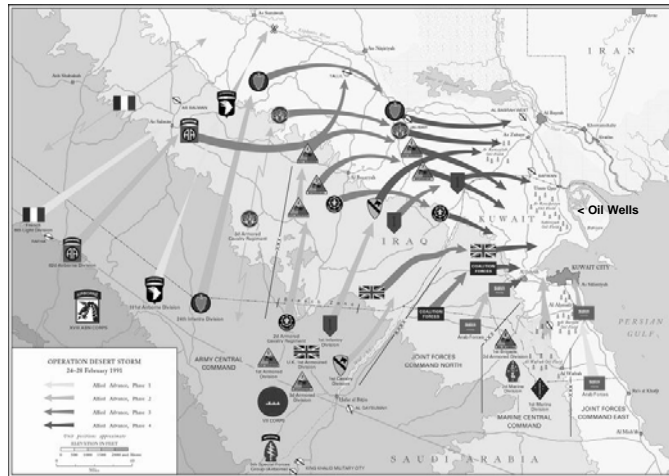
- With its high viscosity and low volatility, VX has the texture and feel of high-grade motor oil. This makes it especially dangerous, as it has a high persistence in the environment. It is odorless and tasteless, and can be distributed as a liquid or, through evaporation, into small amounts of vapor.
- It works as a nerve agent by blocking the function of the enzyme acetylcholinesterase. Normally, an electric nerve pulse would cause the release of acetylcholine over a synapse that would stimulate muscle contraction. The acetylcholine is then broken down to non-reactive substances (acetic acid and choline) by the acetylcholinesterase enzyme. If more muscle tension is needed the nerve must release more acetylcholine. VX blocks the action of acetylcholinesterase, thus resulting in sustained contractions of all the muscles in the body. Sustained contraction of the diaphragm muscle causes death by asphyxiation.

## VX in IRAQ

- Iraq under Saddam Hussein admitted to UNSCOM that it had researched VX, but had failed to weaponize the agent due to production failures. After U.S. and allied forces invaded Iraq, no proof of weaponized VX was found. BUT subsequent investigations after the 2003 invasion of Iraq indicates that Iraq had indeed weaponized VX in 1988 and had dropped three VX-filled bombs on Iran.
- The only countries known to possess VX are the United States and Russia. However, under Saddam Hussein's regime, Iraq was suspected of buying VX; a Sudanese pharmaceutical facility was bombed by the U.S. in 1998 following allegations that it in some way used VX and that the origin of the agent was associated with both Iraq and Al Qaeda.

- The following five slides show troop locations and wind direction data after the fighting period.
- Then there are two slides with anecdotal evidence of a nerve agent exposure based on my own experience of being there.

### Troop Deployments During Desert Storm

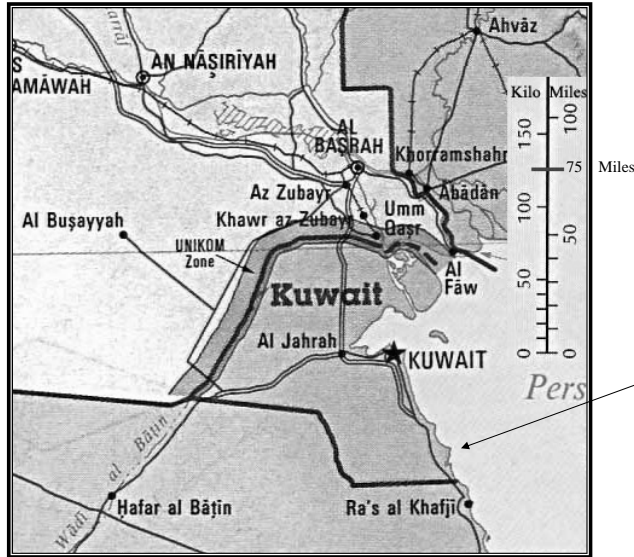


Detail of Troop Deployments in Southeast Iraq and Kuwait during the Desert Storm attack phase.

75 miles from AL JAHRA to BASRA.

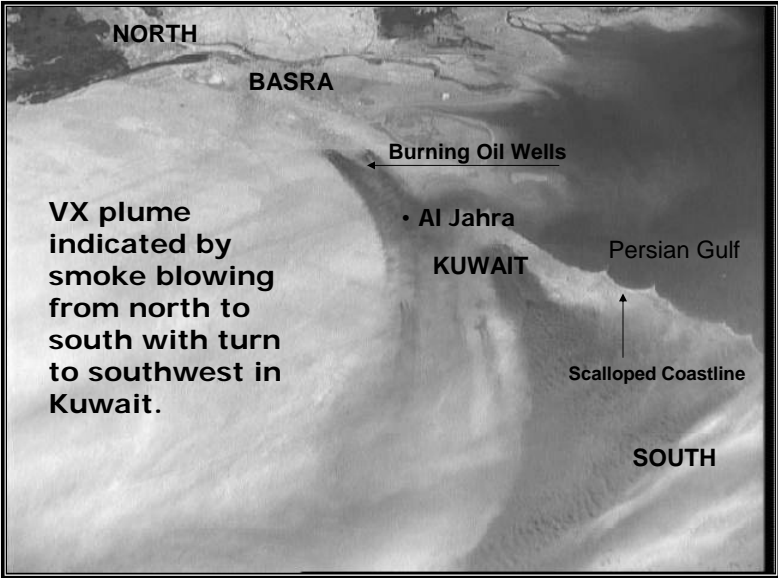


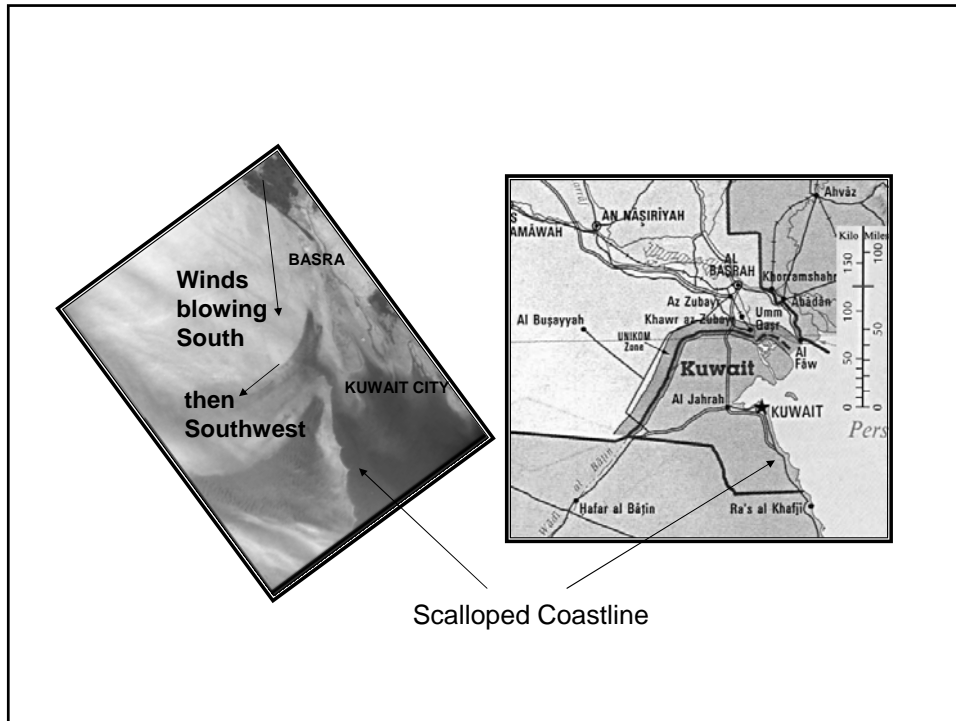
### Basra to Kuwait City – 75 Miles



The coastline below Kuwait has a scalloped appearance, which is noticeable on this map and on the satellite view on the next slide.

### Oil Well Fire Plumes View from Space





On March 15<sup>th</sup>, after the evening meal, everyone in my unit got sick. Some were very sick and went to bed. I was nauseated and dizzy for several hours. We thought it was food poisoning, but our tactical operations center heard that chemical alarms had gone off in some units around us. Our own chemical alarms had been put away a month before, right after the war ended.

Unusually strong north winds blew down on us for a few days.

At that time, Basra, 75 miles to the north, was gassed by Saddam Hussein's helicopters to put down the Shiite uprising, and the nerve agent apparently blew down on us. I acknowledge that it was probably a small dose, but it was enough to set off chemical alarms, and it was enough to make people sick. Even if it was a very small dose by the time it reached us, it was a significant amount – it was enough.

Picture taken out of Humvee window at midday during attack. It was so dark, we could barely see road.  
Picture is of oil well fire to west blowing down on us as we attacked north to Kuwait City, 2nd day.

Based on my experience and symptoms, and what we know of VX,  
I believe the Basra uprising exposed coalition troops to a  
low but significant dose of VX nerve agent.



Soldier on top of captured Iraqi T-72, taken with camera flash at noon time.  
It really was that dark. It was so dark, you could not read a book outside.  
All of these pictures are of the 1st Battalion, 67th Armor Regiment, 2nd Armor Division.

## Gulf War Illness

- This does not mean that Gulf War Illness is *only* caused by nerve agent exposure. But Khamisiyah and Basra could be the most significant gross exposures, and if studied closely, might shed more light on the illnesses that have plagued veterans for so long. These may be the primary causes, which might drive the creation of a case definition.
- As seen on my exposure spreadsheet, a cocktail of exposures affect troops exasperating the medical community's ability to track down a single cause.
- It is possible that other exposures, PB, Pesticides, Depleted Uranium, etc. and a variety of stressors like poor weather, oil well fires, and combat stress, exasperate the gross exposures causing a synergistic effect: Meaning that the combined group of exposures make a person more sick than either one alone.

**The health of Gulf War veterans is in the balance:  
Many are sick, many are dying, and many are still  
struggling with the VA healthcare system.**

**My hope is that the goals of this presentation  
will be promptly acted upon:**

1. DOD verify exposure & notify veterans as done for Khamisiyah
2. GAO study exposure incident and brief DOD and RAC
3. VA notify all vets and VA facilities of this additional exposure
4. RAC promote studies of VX exposure

Thank You

Contact Information: Joel Graves [jgraves@reachone.com](mailto:jgraves@reachone.com) 360-789-5300

# Multiple Sclerosis & Gulf War Veterans

September 14, 2008

Mitchell T. Wallin, MD, MPH

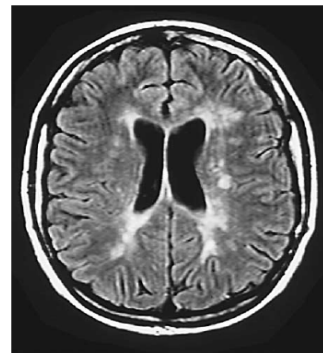
**Clinical Associate Director  
VA MS Center of Excellence East-Baltimore**

**Associate Professor of Neurology  
Georgetown University School of Medicine**



## Multiple Sclerosis

- MS is an inflammatory demyelinating disease of the CNS and the most common progressive neurological disease of young adults
- 350,000-400,000 people with MS in the US
- Current evidence points to an environmental trigger initiating the disease in a genetically susceptible host
  - Epidemiologic evidence
  - Discordance rate in monozygotic twins
  - High CSF IgG and Oligoclonal bands
- Demographic Risk Factors
  - Female sex
  - White race
  - High socioeconomic status
  - Scandinavian ancestry



Axial FLAIR Brain MRI (NEJM, 2000)



## MS and Genetic Susceptibility

- MS is a complex genetic disorder
- Risk for MS is associated with genetic sharing
- Maximal monozygotic twin concordance of 30%
- HLA II (DR15/DQ6) is major genetic risk allele
- Other small effect genes being identified (IL2, IL7)

	Prevalence
General population rate	1/1000
Adoptive siblings	1/1000
First cousin	7/1000
Paternal half sibling	13/1000
Half sibling reared apart	24/1000
Maternal half sibling	24/1000
Full sibling risk	35/1000
HLA identical sibling	80/1000
Sibling in consanguineous mating	90/1000
Child or sibling	197/1000
Offspring conjugal pair	200/1000
Monozygotic twin risk	270/1000

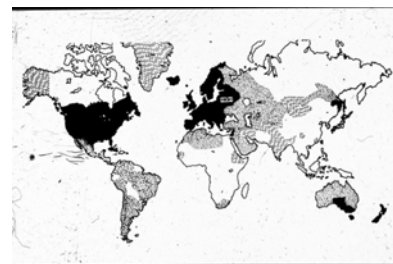
Table: Population-based prevalence rates in relatives of MS probands

Ebers G, Lancet Neurol 2008



## Evidence for Environmental Susceptibility in MS

- Geographic prevalence gradients
  - ◆ Three prevalence zones
    - ☞ Low: < 4 per 100K
    - ☞ Medium: 5-29 per 100K
    - ☞ High: > 30 per 100K
- High Risk Zones
  - ◆ Europe
  - ◆ North America
  - ◆ So. Australia



Kurtzke, 2004



## MS Etiology- 2 Theories

- Both argue MS is a rare complication of a widespread microbe
  - ◆ “Prevalence hypothesis”: MS is triggered by a microbe more common in geographic regions of high risk
  - ◆ “Hygiene hypothesis”: MS is triggered by a late age infection of a common microbe

## Evidence for Environmental Susceptibility in MS

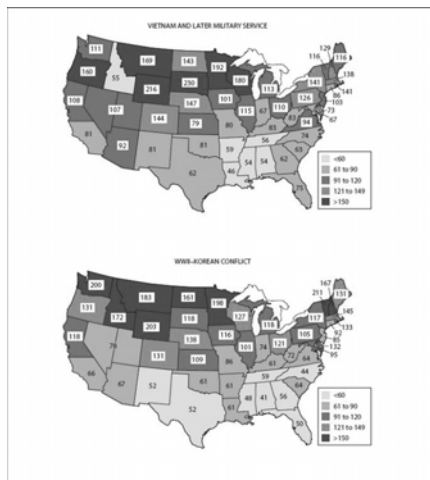
- Epidemics of MS
  - ◆ Faroe Islands
- Migration alters MS risk
  - ◆ Low Prevalence zone → High Prevalence Zone
  - ◆ High Prevalence zone → Low Prevalence Zone
  - ◆ Israel

### Adjusted case-control ratios for MS by race and sex at EAD (Wallin, 2004)

Race-sex category	WWII-KC Cohort		Vietnam and later Cohort	
	# of MS cases	Case-control ratio (95% CI)	# of MS cases	Case-control ratio (95% CI)
White female	182	1.84 (1.42 – 2.36)	604	2.79 (2.44-3.19)
Black female	4	1.33 (0.30 – 26.3)	123	2.65 (1.38-3.52)
Other race-female	2	----	16	3.31 (1.46-7.50)
White male	4,923	1.03 (0.97 – 1.08)	3,758	0.97 (0.91-1.01)
Black male	177	0.45 (0.38 – 0.54)	415	0.64 (0.43-0.53)
Other race-male	17	0.23 (0.14 – 0.39)	35	0.29 (0.21-0.61)
<b>TOTAL</b>	<b>5,305</b>	<b>1.00</b>	<b>4,951</b>	<b>1.00</b>



### Case-control Ratios for MS by US State at EAD



Diffusion of MS Risk





## 1990-1991 Gulf War

- Conflict between Iraq & coalition forces from 34 nations led by US to liberate Kuwait
- Nearly 700,000 US troops deployed to the war theater
- Gulf War Conflict: 8/1/90-7/31/91
- 42 days of combat started January 17, 1991 with 148 US troops killed
- \$60-70 Billion to deploy and maintain US troops



Veterans Affairs  
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East

## Gulf War Veterans and MS



### Senator Murray Introduces New Bill to Help More Veterans with Multiple Sclerosis

Murray's Bill Addresses the High Rate of MS Among Veterans;  
Wins Endorsement of MSVETS and National Gulf War Resource Center

Murray's Legislation Lifts the VA's Arbitrary 7-year Limit to Qualify for Automatic VA Benefits  
For Immediate Release:

Tuesday, December 20, 2005

(Washington, D.C.) – Today, U.S. Senator Patty Murray (D-Wash) introduced new legislation to help more veterans who have Multiple Sclerosis (MS) qualify for disability benefits from the Department of Veterans Affairs (VA). A growing number of veterans from the first Gulf War are now developing symptoms of MS, but they often face an uphill battle in obtaining disability benefits

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# ALS and Gulf War Veterans

(Neurology, September 2003)

Articles

## Occurrence of amyotrophic lateral sclerosis among Gulf War veterans

R.D. Horner, PhD; K.G. Karmins, PhD; J.R. Foussner, MD, MPH; S.C. Grambow, PhD; J. Hoff-Lindquist, MStat; Y. Harati, MD; H. Mizumoto, MD, DSt; R. Pascuzzi, MD; P.S. Spencer, PhD; R. Tim, MD; D. Howard, MSFH; T.C. Smith, MS; M.A.K. Syas, MD, MPH; C.J. Coffman, PhD; and E.J. Kasarska, MD, PhD

## Excess incidence of ALS in young Gulf War veterans

Robert W. Haley, MD

- Horner, et al used active & passive surveillance to determine incidence rate of ALS 1990-2000
- 107 cases among 2.5 million veterans; incidence 0.43 per 100,000 persons/yr
- RR ALS 1.9 in GW Vets compared with nondeployed controls
- Haley, et al showed a higher incidence rate in deployed GW Veterans < 45 yrs

Veterans Affairs  
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# MS in Gulf War Veterans

- Population survey of MS in Kuwait 1993-2000
- Incidence rate increased from 1.05/100,000 in 1993 to 2.62 per 100,000 in 2000
- Prevalence changed from 6.7 to 14.8 per 100,000
- Most dramatic changes seen in Kuwaiti natives

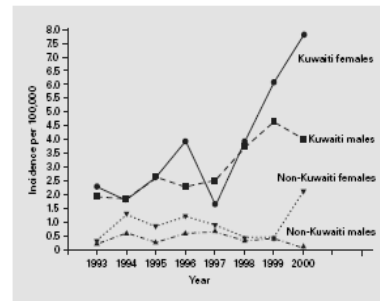


Fig. 1. Incidence of MS in Kuwait according to sex and nationality, 1993-2000.

Alshubaili, Eur Neurol 2005

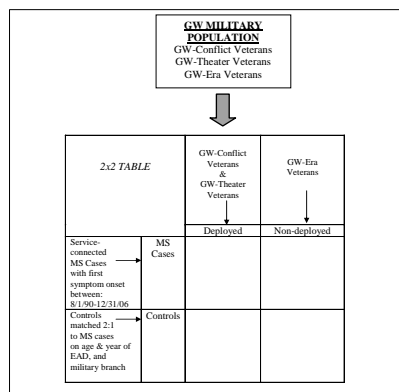
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## MS in Gulf War Veterans Study: Deployment Status among the MSCoE Data Repository 1998-2003

Deployment Status	Frequency (%)	Age (SD) <sup>1</sup> Years	Male <sup>2</sup> (%)	SC-MS (%)	Deceased (%)
GW-Conflict: deployed 8/90 – 7/91	414 (2.6)	29.9 (7.1)	77.3	67.4	2.7
GW-Theater: deployed on or after 8/91	157 (1.0)	26.3 (6.8)	86.6	82.2	4.5
GW-Era: active duty - not deployed	1,884 (11.8)	31.8 (8.1)	66.8	67.3	3.9
Not on active Duty	13,481 (84.6)	48.1 (11.5)	89.7	37.8	21.2
<b>VA MSCoE MS Data Repository Cohort</b>	<b>15,936 (100)</b>	<b>45.6 (12.6)</b>	<b>86.6</b>	<b>42.5</b>	<b>18.5</b>

## MS in Gulf War Veterans Study

- **Primary Hypothesis:**
  - ◆ Deployed GW veterans will be at increased risk for developing MS compared with non-deployed GW veterans.
- **Secondary Hypothesis**
  - ◆ In-theater exposure characteristics of deployed GW veterans will be associated with an increased risk of developing MS.

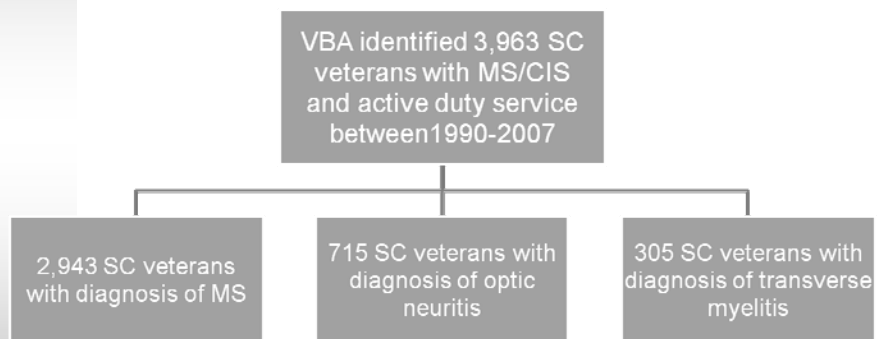


## MS in Gulf War Veterans Study

- Case-control study design: 2 pre-illness military controls matched to each MS service-connected case on:
  - ◆ age and date of entry into active duty
  - ◆ service branch
- Deployed GW veterans will be at increased risk for developing MS compared with non-deployed GW veterans:
  - ◆ OR stratified by demographic & clinical variables
  - ◆ Logistic regression analysis
  - ◆ Kaplan-Meier curve to assess 15-year risk of developing service-connected MS diagnosis (deployed vs. non-deployed)
- In-theater exposure characteristics of deployed GW veterans will be associated with an increased risk of developing MS.
  - ◆ Logistic regression analysis based on existing troop models of exposure
    - Khamisiyah sarin exposure and troop location
    - Oil Smoke plume model



## MS in Gulf War Veterans Study Cohort



## Current variables for abstraction

**Demographics:** DOB, Race, Ethnicity, EAD, RAD, location at birth and EAD, marital status, living situation, education and military occupation/pay grade

**Clinical:** Date of MS symptom onset, MS diagnosis adjudication (McDonald criteria), clinical subtype, CSF, MRI, evoked potentials, DSS with functional systems (C&P exam and most recent), % service connection, PMH, DMT use, family history autoimmune disease

**Environmental:** Deployment, branch, rank, military occupation, immunizations, exposure to the following: sarin, oil-well fires, agent orange and miscellaneous



## MS in Gulf War Veterans Study

Table 5. Study variables with corresponding data source

Variables	Data Source
Location at birth (Categorize as US North/Middle/South based on VNEM cohort)	C-folder & National Personnel Records Center
Location at entry into active duty (Categorize as US North/Middle/South based on VNEM cohort)	Defense Manpower Data Center & National Personnel Records Center
Race/Ethnicity/Gender <sup>a</sup>	Defense Manpower Data Center & VA Computerized Patient Record System
Socioeconomic status: education, employment, annual income estimate (stratify into 4 tiers)	Defense Manpower Data Center & VA Computerized Patient Record System
MS Service-connection status	Beneficiary Identification and Records Locator Subsystem, C-folder
Date of MS onset, MS subtype <sup>b</sup> , clinical information, death	C-folder, VA Computerized Patient Record System, VA MSCoE Data Repository, Beneficiary Identification and Records Locator Subsystem
GW, Bosnia/Kosovo, and OEF/OIF deployment status	VA Environmental Epidemiology/WRIISC Databases
Exposure to sarin	VA Environmental Epidemiology/WRIISC Databases
Exposure to oil-well fires	VA Environmental Epidemiology/WRIISC Databases

<sup>a</sup>According to a recent VA directive, race is categorized as: African American, White, Asian, Native American/Eskimo and ethnicity as: Hispanic/Latino or non-Hispanic/Latino<sup>79</sup>

<sup>b</sup>MS subtypes will be classified at onset according to the standard Lublin criteria: relapsing-remitting vs. primary progressive<sup>64</sup>



## Potential Risk Factors for MS in Gulf War Veterans

- Vaccinations
  - ◆ Anthrax (Kerrison, 2002)
  - ◆ Hepatitis B (Hernán, 2004)
- Viral infections
  - ◆ Parvovirus B19 aplastic crisis 1991 in Gulf region (Mallouh, 1995)
- CNS toxins
  - ◆ Sarin
  - ◆ Pyridostigmine bromide
  - ◆ Organic solvents (Riise, 2002)
- Air pollutants (Oikonen, 2003)



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## Assessment of MS risk in Veterans

- VHA system evaluates only 30-40% veterans with MS
- Case-control studies
  - ◆ Service-connected population
  - ◆ VALOMS Cohort
  - ◆ MSCoE Occupational-Environmental Survey
  - ◆ DoD Serum Repository
- Surveillance of DoD and VA population
  - ◆ Existing registries (e.g. NARCOMS)
  - ◆ Population-based surveys
    - ☞ Prevalence
    - ☞ Incidence

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## MS Epidemiology Research Group

- VAMC/MSCoE
  - ◆ Parisa Coffman, MPH
  - ◆ Chichi Onyemaechi, BS
  - ◆ Heidi Maloni, PhD
  - ◆ Joel Culpepper, PhD
  - ◆ Jodie Haselkorn, MD, MPH
  - ◆ John Kurtzke, MD
- VA Environmental Epidemiology
  - ◆ Han Kang, PhD
  - ◆ Clare Mahan, PhD
- NIH-NINDS-Neuroimmunology Branch
  - ◆ Steve Jacobson, PhD
- DoD Serum Repository
  - ◆ Steven Tobler, MD

*Funding: VA Merit Review, NMSS*



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## **Overview of the Congressionally Directed Medical Research Programs (CDMRP)**

**Presented to  
the Research Advisory Committee  
on Gulf War Veterans' Illnesses  
by  
E. Melissa Kaime, MD, FACP  
Captain, Medical Corps, USN  
Director, CDMRP**


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## **Introduction**

- ◆ **Overview of the CDMRP**
- ◆ **Gulf War Illness Research Program (GWIRP) Synopsis**
  - ❖ **Priority Areas**
  - ❖ **2006 Awards**
  - ❖ **Fiscal Year 2008 (FY08) Funding Mechanisms**

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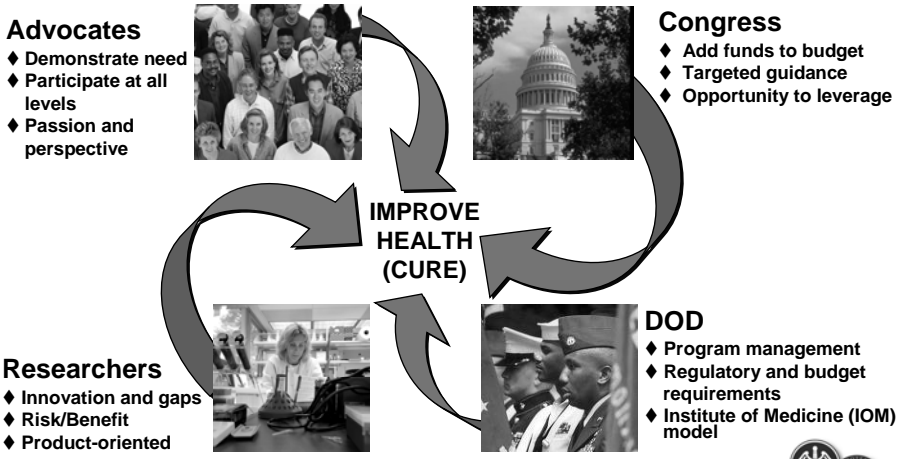
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## Partnerships



- Advocates**
  - ◆ Demonstrate need
  - ◆ Participate at all levels
  - ◆ Passion and perspective
- Congress**
  - ◆ Add funds to budget
  - ◆ Targeted guidance
  - ◆ Opportunity to leverage
- DOD**
  - ◆ Program management
  - ◆ Regulatory and budget requirements
  - ◆ Institute of Medicine (IOM) model
- Researchers**
  - ◆ Innovation and gaps
  - ◆ Risk/Benefit
  - ◆ Product-oriented


**IMPROVE HEALTH (CURE)**

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## CDMRP Unique Features

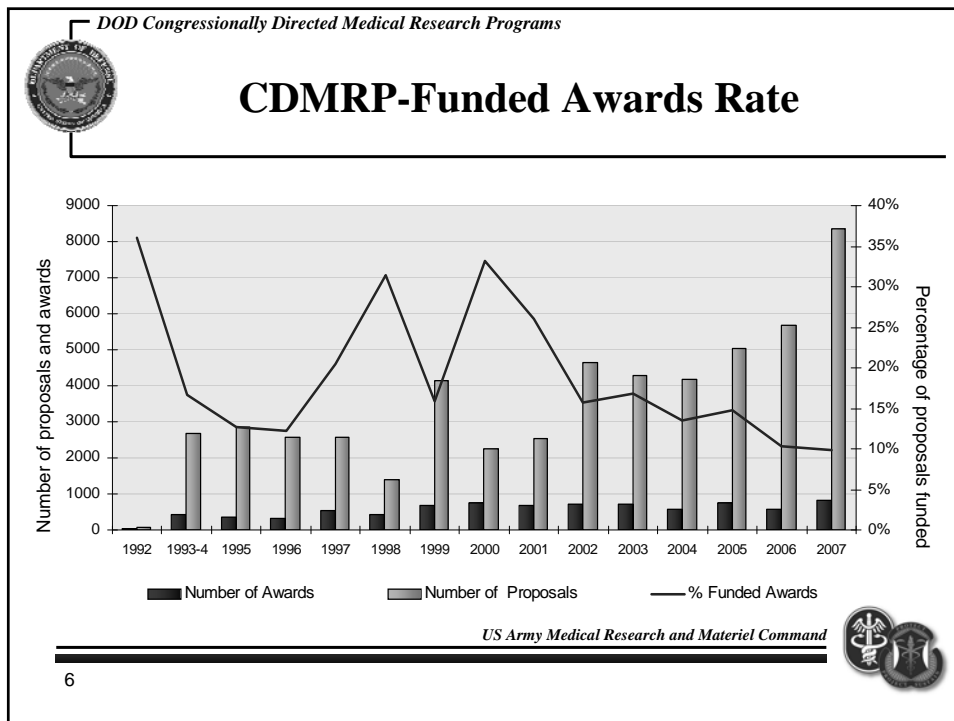
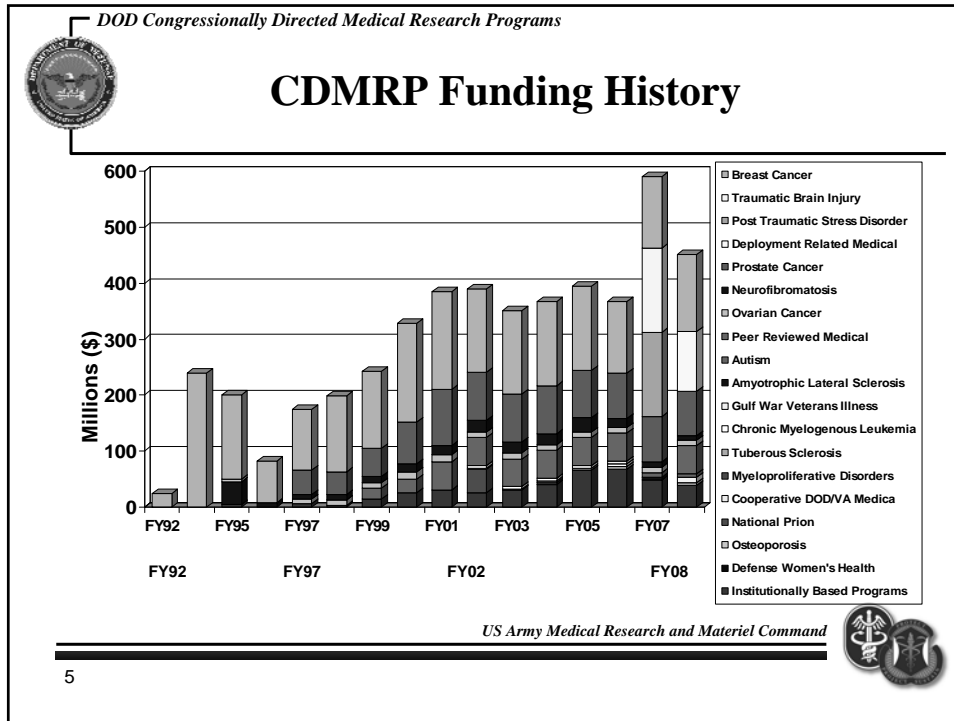
- ◆ Funds added to the Department of Defense budget by Congress (disease-specific)
- ◆ Two-tier formal review of proposals – IOM model
- ◆ Consumer advocates involved throughout process
- ◆ Vision is adapted yearly: Facilitates rapid change to address research gaps, develop new award mechanisms, and devise investment strategy
- ◆ Fund highly innovative research
- ◆ Funding flexibility
  - ❖ No “pay line”
  - ❖ Second level review based on impact, relevance, and portfolio balance
  - ❖ No out-year budget commitments

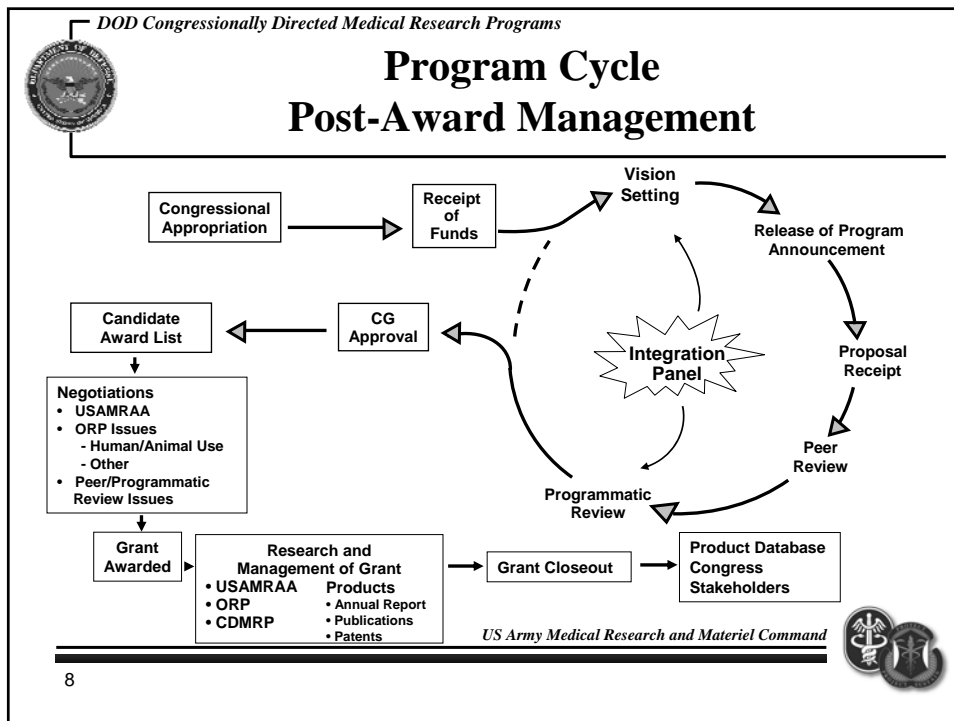
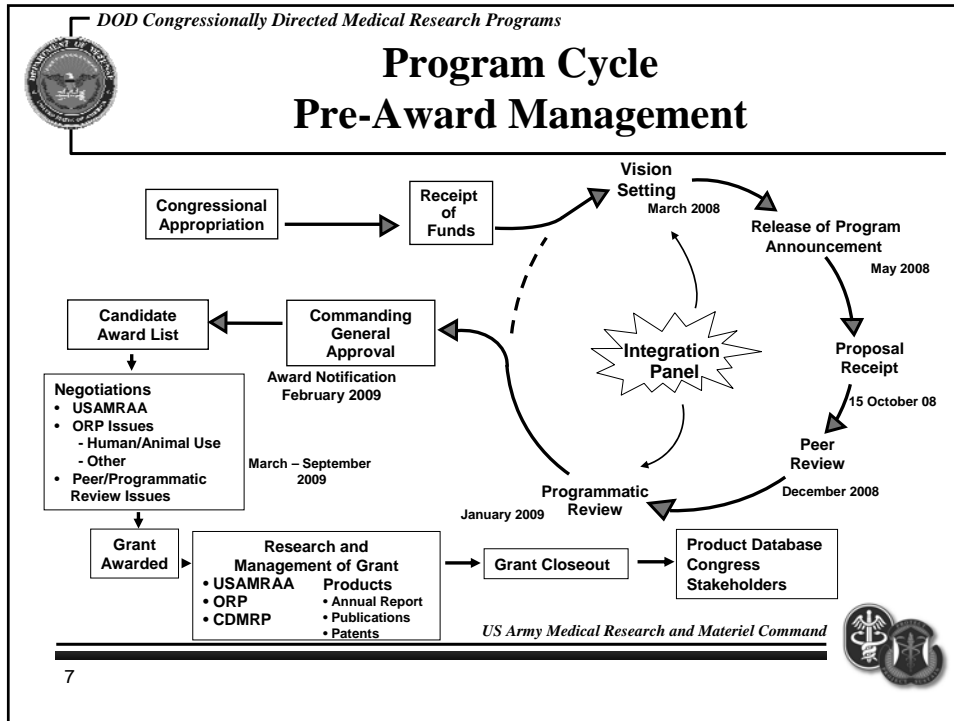


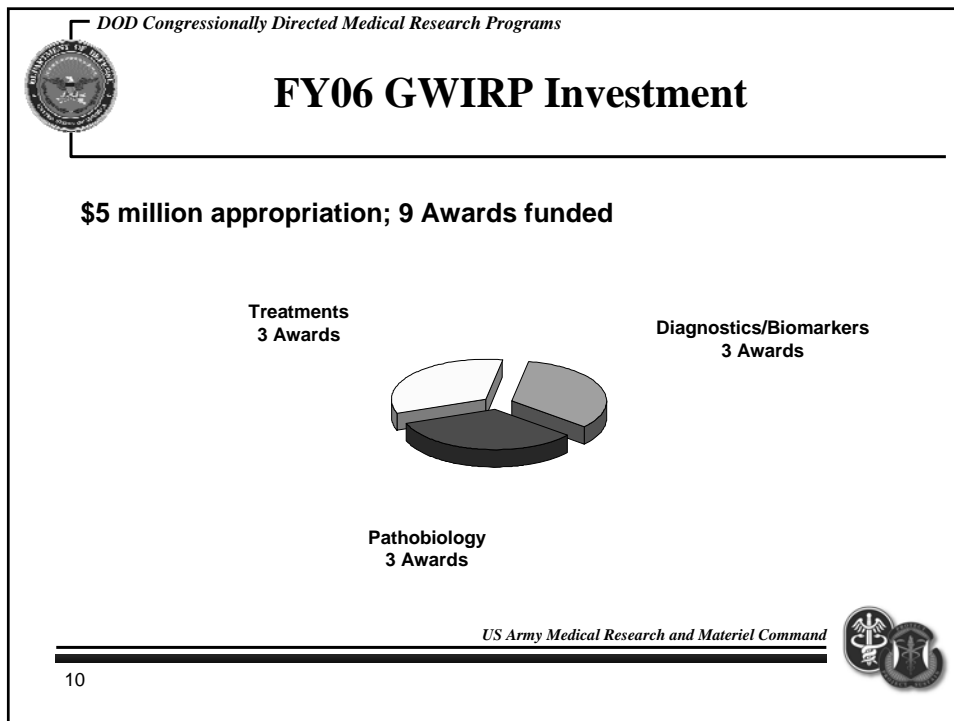
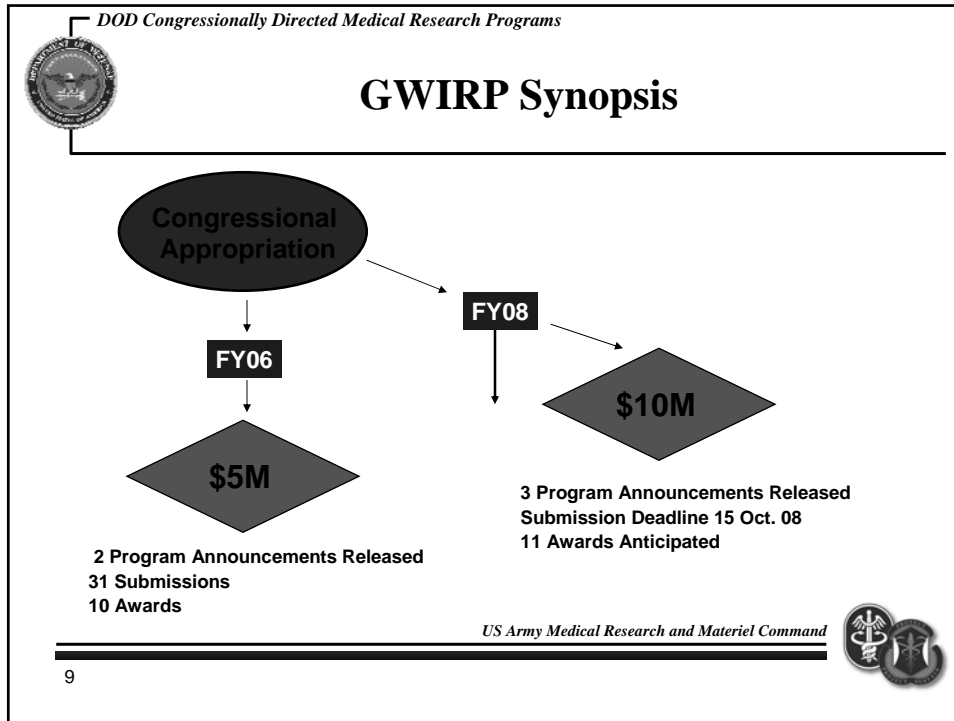
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## **FY06 GWIRP Awards - Treatments**

- ◆ Dr. Julia Golier at the Bronx Veterans Medical Research Foundation is investigating a new use for mifepristone in a clinical trial to determine if its glucocorticoid receptor antagonistic properties can improve the health of Gulf War Veterans with Chronic Multi-symptom Illness while also helping to elucidate neuroendocrine mechanisms of the disease by studying changes in the hypothalamic-pituitary-adrenal axis.
- ◆ Dr. Beatrice Golomb of the University of California is exploring the potentially beneficial effects of coenzyme Q10 for symptom reduction in Gulf War Illness victims and how the enzyme may improve the overall quality of life for veterans.
- ◆ Dr. William Meggs at East Carolina University plans to conduct a randomized controlled trial to determine preliminary efficacy of environmental medicine therapy in ill GW veterans and determine if markers of inflammation and autonomic function are affected by this intervention.

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## **FY06 GWIRP Awards - Biomarkers**

- ◆ Dr. Mariana Morris at Wright State University is using an animal model of sarin exposure to study biomarkers for GWI, including cardiovascular function and autonomic balance, then evaluating commercially available treatments with the model
- ◆ Dr. James Baraniuk at Georgetown University is evaluating carnosine dipeptidase 1 (CNDP1), initially found more often in GWI subjects than healthy controls, as a biomarker for GWI, and learning more about its function and potential as a new treatment
- ◆ Dr. Christopher Phillips at the Naval Health Research Center is studying the influence of the liver enzyme paraoxonase, organophosphate pesticide exposure, and pyridostigmine bromide medication on the likelihood of increased post-war symptom reporting in deployed and non-deployed Seabee GW veterans.

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## **FY06 GWIRP Awards – Pathobiology**

- ◆ Dr. Kimberly Sullivan at the Boston University School of Medicine is investigating cognitive function and other health effects in Gulf War veterans exposed to organophosphate pesticides
- ◆ Dr. Peter Baas of Drexel University has developed an experimental paradigm to test the hypothesis that environmental toxins adversely affect the transport of microtubules within nerves which may lead to refinement of approaches for potential therapies for GWI-related neurodegeneration.
- ◆ Dr. Stephen Lasley of the University of Chicago-Illinois is examining the possibility that long-term exposure to depleted uranium (DU) induces oxidative stress in hopes to uncover the mechanisms underlying DU neurotoxicity as well as the promise of NMDA receptor antagonist(s) to diminish DU effects on glutamatergic function and oxidative stress.

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## **FY08 National Defense Authorization Act**

**HR 1585 Conferees directed the Secretary of the Army to utilize the authorized funding ... to undertake research on Gulf War Illnesses. Conferees also directed that activities under the Gulf War Illnesses program include:**


- ◆ **Studies of treatments for the complex of symptoms known as “Gulf War Illness”**
- ◆ **No studies based on psychiatric illness and psychological stress as the central cause**
- ◆ **Competitive selection and peer review to identify research with the highest technical merit and military value**
- ◆ **Coordinate with similar activities in the VA and NIH**

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## GWIRP Priority Areas


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- ◆ Identification of effective treatments for GWI
- ◆ Improved diagnostic testing for GWI
- ◆ Improved understanding of GWI pathobiology




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## GWIRP FY08 Investment Strategy

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<u>Award Mechanism</u>	<u>Funds Allocated</u>	<u>Anticipated</u>
Innovation Based <b>Idea Award</b>	<b>\$1.5M(18%)</b>	<b>4</b>
<b>Investigator-Initiated Research Award</b>	<b>\$5.0M(59%)</b>	<b>5</b>
Translational Research <b>Clinical Trial Award</b>	<b>\$2.0M(23%)</b>	<b>2</b>
<b>Totals</b>	<b>\$8.5M (100%)</b>	<b>11</b>

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## Idea Award

***Intent:***

To sponsor highly innovative, high-risk/high-reward research that could ultimately lead to critical discoveries or major advancements in the treatment, diagnosis and understanding of Gulf War Illness

***Eligibility and Award Information:***

- ◆ Investigators at all academic levels may apply
- ◆ Maximum of \$100K per year in direct costs for a period of up to 2 years, plus indirect costs as appropriate
- ◆ Inclusion of preliminary data is not allowed
- ◆ Clinical Trials not allowed

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## Investigator-Initiated Research Award

***Intent:***

To support research to identify effective treatment for Gulf War Illness, improve its diagnosis, and better understand its pathobiology

***Eligibility and Award Information:***

- ◆ Investigators at any academic level may apply
- ◆ Maximum of \$200K per year in direct costs for up to 3 years, plus indirect costs as appropriate
- ◆ Requires preliminary data, although it may be from outside the field of Gulf War Illness research
- ◆ Clinical Trials not allowed


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## Clinical Trial Award

***Intent:***


To support rapid execution of clinical trials with a potential for significant impact on the health and lives of Veterans with Gulf War Illness

***Eligibility and Award Information:***

- ◆ Investigators at all academic levels may apply
- ◆ Maximum of \$250K per year in direct costs for up to 3 years, plus indirect costs as appropriate
- ◆ Requires preliminary data, although it may be from outside the field of Gulf War Illness research


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## FY08 GWIRP Integration Panel Members

**Lea Steele, Ph.D. (Chair)**  
Kansas State University

**Sam Donta, M.D.**  
Donta Infectious Diseases

**Anthony Hardie**  
Wisconsin Department of Veterans Affairs

**COL Cornelius Maher, M.D., Ph.D.**  
Army Medical Command


**CAPT Kerry Thompson, Ph.D.**  
Naval Health Research Center

**Mary Nettleman, M.D., M.S.**  
Michigan State University

**MAJ David Watson, Ph.D.**  
US Air Force Research Laboratory

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 **http://cdmrp.army.mil**

Department of Defense  
**Congressionally Directed Medical Research Programs**

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Home » **Research Programs** » Gulf War Illness

Search Site:

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### Gulf War Illness

**Vision**  
Improve the health and lives of veterans who have Gulf War Illness

**Mission**  
Fund innovative research to identify effective treatments for the complex symptoms known as Gulf War Illness, improve its diagnosis, and better understand its pathobiology



The OWRP was established in FY94 to study the health effects of warfighters deployed in the 1991 Persian Gulf War. From FY94 to FY05, the OWRP was managed by the USAMRIID Military Operational Medicine Research Program (MOMRP). In FY02, under direction from the Assistant Secretary of Defense (Health Affairs), the OWRP shifted its focus from retrospective assessment of Gulf War Veterans' illnesses to prospective protection of current and future service members put into operational environments similar to those of the 1991 Persian Gulf deployment. The CDMRP assumed management responsibility for the OWRP in FY06. The two key priority areas for the FY06 OWRP were "identification and evaluation of currently available treatments" and "identification of objective indicators of pathology that distinguish it from healthy veterans." Proposals were requested through two award mechanisms: Investigator-Initiated Research and Exploration-Hypothesis Development Awards.

- [Find Out Opportunities](#)
- [Search Awards](#)
- [Information Events](#)
- [Peer Review Participants](#)

**Congressional Appropriations**

- \$5.9 million in FY06
- \$10 million in FY08

**Funding Summary**

- 9 awards in FY06



**Gulf War Illness News**

FY06 OWRP Funding Opportunities Now Available

[More News...](#)

**Research Highlights**

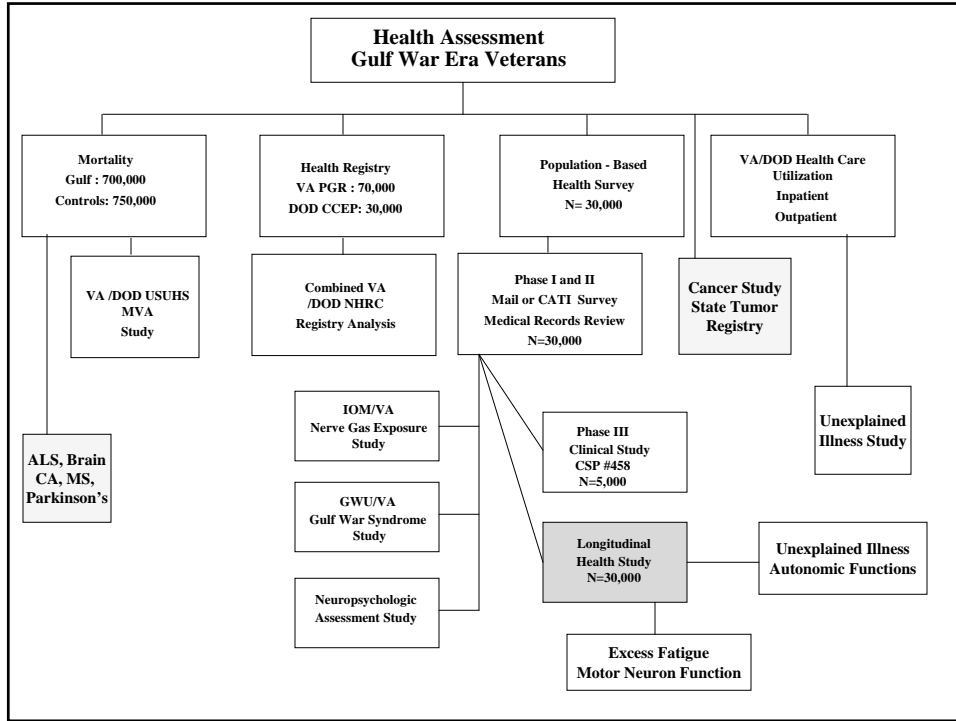
Coming Soon

[Previous Highlights...](#)

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## **Neurological and all-cause mortality among US veterans of the Persian Gulf War: 13-year follow-up**

Shannon Barth, MPH; Han Kang, DrPH;  
Mitchell Wallin, MD; Tim Bullman, MS



## **Background**

- 13 year follow-up study comparing GW and non-GW veterans
  - All-cause mortality
  - Focus on neurological deaths
    - ALS (amyotrophic lateral sclerosis)
    - MS (multiple sclerosis)
    - Parkinson's disease
    - Brain cancer
- This cohort was previously followed-up at 2 and 7 years.



## Objectives

- To determine vital status through 2004 of GW and non-GW veterans in this cohort
- To determine cause of death of deceased
- To compare mortality between GW and non-GW veterans
- To compare mortality between veterans and the US population
- To determine the association between neurological and other cause-specific deaths and military, exposure, and demographic characteristics



## Cohort description

- GW veterans: 621,902 U.S. veterans who were in the Persian Gulf before the armed conflict ended on March 1, 1991
- Non-GW veterans: 746,248 veterans from a stratified random sample of all military personnel (active duty, reserves or National Guard) who served during the GW but were not in theater



## Measures

- Dependent variables:
  - All causes of death
  - Disease-related causes (infectious and parasitic diseases, all cancers, diseases of circulatory system, respiratory system, digestive system, neurological diseases)
  - External causes (all accidents, suicide, homicide)
- Independent variables:
  - Demographics (date of birth, race, marital status during war, gender, military rank, branch of service, deployment date, unit component)
  - Potential nerve gas exposure at Khamisiyah among Army GW veterans (1 day, 2 or more days, not exposed)
  - Potential oil well fire smoke exposure among Army GW veterans (considered exposed if at least 0.26 mg/m<sup>3</sup> of total suspended particulate)



## Methods

- Determine vital status through December 31, 2004 using BIRLS and SSA Death Master File
- Determine ICD-9 cause of death using VA Regional Office, Federal Records Center, or NDI
- Collect medical records for neurological disease deaths (ALS, MS, brain cancer, Parkinson's disease) through VA records or next of kin
- Determine accuracy of death certificate cause of death by analyzing medical records




## Statistical analyses

- Cox proportional hazard models were used to calculate adjusted rate ratios (aRR) and 95% confidence intervals (95% CI) for cause-specific mortality while controlling for potential confounding variables
- Veteran mortality compared to US population by calculating standardized mortality ratios (SMR) and 95% CI




## Results

- 10,869 deaths in the GW veteran group
- 14,716 deaths in the non-GW veteran group
- Cause of death missing:
  - 7.08% GW vets
  - 7.41% non-GW vets
- GW vets more likely to be male, slightly younger, active duty
- GW and non-GW vets similar in race, branch of service, marital status at deployment



### Risk of neurological disease mortality among GW veterans compared to non-GW veterans

	Total deaths	GW veterans n= 621,901	Non-GW veterans n=746,247	Adjusted rate ratio	95% CI
ALS	61	23	38	0.96	0.56, 1.62
MS	19	6	13	0.61	0.23, 1.63
Parkinson's disease	11	3	8	0.71	0.17, 2.99
Brain cancer	372	144	228	0.90	0.73, 1.11

- 
- ### Cause-specific mortality adjusted rate ratios (aRR)
- Compared to non-GW veterans, GW veterans had
    - Lower risk of death due to:
      - Disease-related causes (aRR = 0.94, 95% CI: 0.91, 0.98)
        - Infectious diseases (aRR = 0.58, 95% CI: 0.49, 0.68)
          - » HIV (aRR = 0.29, 95% CI: 0.21, 0.39)
    - Higher risk of death due to:
      - All accidents (a RR = 1.07, 95% CI: 1.01, 1.13)
        - Motor vehicle accidents (aRR = 1.08, 95% CI: 1.01, 1.15)





### Cause-specific mortality adjusted rate ratios stratified by gender

- Males: GW vs. non-GW veterans
  - All causes (aRR = 0.97, 95%CI=0.95, 0.998)
  - Disease-related causes (aRR = 0.93, 95% CI: 0.90, 0.97)
    - Infectious diseases (aRR = 0.56, 95% CI: 0.47, 0.68)
      - HIV (aRR = 0.29, 95% CI: 0.21, 0.39)
  - All accidents (aRR = 1.06, 95% CI: 1.01, 1.12)
- Females: GW vs. non-GW veterans
  - All causes (aRR = 1.15, 95% CI: 1.03, 1.28)
  - Digestive system diseases (aRR = 2.05, 95% CI: 1.09, 3.84)
  - External causes (aRR = 1.32, 95% CI: 1.09, 1.60)
    - Motor vehicle accidents (aRR = 1.44, 95% CI: 1.06, 1.97)



### Risk of suicide among Gulf War veterans compared to non-GW veterans based on marital status at time of deployment

	Females		Males	
	Adjusted rate ratio	95% CI	Adjusted rate ratio	95% CI
Married	2.09	1.20, 3.63	0.95	0.86, 1.06
Not Married	0.96	0.58, 1.58	0.97	0.88, 1.07



## Mortality comparison between GW and non-GW veterans and US population

- No increased risk of brain cancer, ALS, MS, Parkinson's disease deaths among veterans compared to US population  
Female GW veterans had greater risk of suicide compared to female US population (SMR = 1.60, 95% CI: 1.17, 2.13)
- Among married females, GW veterans had increased risk of suicide compared to married US female population (SMR = 1.89, 95% CI: 1.21, 2.82)
- Not-married non-GW females also had increased risk for suicide compared to not-married female US population (SMR = 1.43, 95% CI: 1.06, 1.87)



## Oil well fire smoke and nerve gas at Khamisiyah exposures among Army Gulf War veterans

- 322,249 Army GW veterans total
- Exposure to nerve gas at Khamisiyah
  - 84,328 exposed for 1 day
  - 14,078 exposed for 2 or more days
- Oil well fire smoke exposure
  - 123,478 exposed
- Approximately 13% of Army GW veterans were exposed to both oil well fire smoke and nerve agents at Khamisiyah




## Brain cancer mortality risk among Army GW veterans exposed to oil well fire smoke or nerve gas at Khamisiyah

- Exposure to oil well fire smoke
  - aRR = 1.67, 95% CI: 1.05, 2.65
- Exposure to nerve gas at Khamisiyah for 1 day
  - aRR = 1.42, 95% CI: 0.87, 2.33
- Exposure to nerve gas at Khamisiyah for 2 or more days
  - aRR = 2.71, 95% CI: 1.25, 5.87




## Brain cancer mortality risk among Army GW veterans exposed to oil well fire smoke and nerve gas at Khamisiyah

- Exposure to nerve gas at Khamisiyah (controlling for oil well fire smoke exposure)
  - 1 day exposure: aRR = 1.42, 95% CI: 0.87, 2.33
  - 2 days exposure: aRR = 2.71, 95% CI: 1.25, 5.87
- Exposure to oil well fire smoke (controlling for nerve gas at Khamisiyah)
  - 1 day exposure: aRR = 1.59, 95% CI: 0.98, 2.59
  - 2 days exposure: aRR = 1.81, 95% CI: 0.998, 3.27



### Medical records review results

	Total medical records collected	Confirmed	Probable	Misclassified
ALS	26	14	7 suspected, 2 probable, 2 possible	1
MS	13	6	3 possible	4
Parkinson's disease	7	0	4 probable, 2 possible	1
Brain cancer	238	206	13	19

- 
- ### Brain cancer mortality rate ratios after medical record review
- Total sample
    - Removed 19 misclassified brain cancer cases
      - aRR = 0.95, 95% CI: 0.76, 1.18
    - Removed 19 misclassified brain cancer and 13 probable cases
      - aRR = 0.99, 95% CI: 0.79, 1.23



## Brain cancer mortality rate ratios among Army GW veterans after medical record review

- Army GW veterans, nerve gas exposure at Khamisiyah (controlling for oil well fire smoke exposure)
  - 1 day exposure:
    - Removed 2 misclassified cases of brain cancer
      - aRR = 1.40, 95% CI: 0.85, 2.31
    - Removed 2 misclassified and 1 probable cases of brain cancer
      - aRR = 1.35, 95% CI: 0.81, 2.24
  - 2 days exposure:
    - Removed 2 misclassified cases of brain cancer
      - aRR = 2.79, 95% CI: 1.28, 6.04
    - Removed 2 misclassified and 1 probable cases of brain cancer
      - aRR = 2.79, 95% CI: 1.28, 6.04



## Discussion

- Since the last follow-up through 1997, there have been few changes in mortality risk among GW and non-Gulf veterans
- The risk of death due to motor vehicle accidents is still higher among GW versus non-GW women, though no longer statistically significant among GW versus non-GW men
- Female GW veterans had increased risk of death due to digestive diseases
- Married female GW veterans had increased risk for suicide
- No increased neurological disease mortality risk for GW veterans compared to non-GW veterans
- Deployed Army GW veterans potentially exposed to nerve agents at Khamisiyah, Iraq had an increased risk of mortality due to brain cancer.



# Estimates of Cancer Prevalence in Gulf Veterans Using State Registries

Jessica Maillard, MPH; Han Kang, DrPH;  
Paul Levine, MD; Clare Mahan, PhD;  
Samuel Simmens, PhD; Heather Young, PhD



## Study Purpose

- Past mortality studies of Gulf War and non-Gulf veterans have not suggested excess deaths due to cancer
- Because not all cancers are fatal, mortality studies insufficient to examine cancer in this group
- Recommendation of long term study to investigate cancer risk



## Objectives

- Primary hypothesis is that deployment to the Persian Gulf in 1990-1991 is associated with an increased incidence of specific malignancies
- Aim 1: To assess and compare the relative prevalence, distribution, and characteristics of cancer among Gulf War veterans with non-Gulf War veterans
- Aim 2: To assess demographic, military, or other characteristics associated with cancer



## Study Population

- Files obtained from the DoD Defense Manpower Data Center (DMDC)
- Gulf subjects
  - 621,902 veterans who arrived in the Persian Gulf between August 2, 1990 and March 1, 1991
  - entire population deployed during time frame
- Non-gulf subjects
  - 746,248 non-Gulf control subjects
  - stratified random sample of all military personnel who served during the time of conflict but were not deployed to the Gulf region



## Study History

- Pilot study
  - Linkages with NJ and DC
  - Performed in 1999 with results published in 2005
  - Significant increase in testicular cancer
- Follow-up study allowed match with six additional states
  - Linkages with CA, FL, IL, MD, NY, TX
  - Performed in 2002-2004 with results presented at September 2005 RAC meeting
  - Interim results not significant



## Current Study Efforts

Current effort expands data collection to 28 total state cancer registries

- Kept previous data from FL, IL, MD, NJ, NY
- Updated linkages with CA, DC, TX
- Completely new linkages with AL, AZ, CO, CT, GA, IN, IA, KY, MA, MI, NC, OH, OK, OR, PA, SC, TN, VA, WA, WI





## Methodology

- File prepared and sent to each state cancer registry
  - Variables available for matching included name, social security number, date of birth, date of death (if applicable), gender, and race
  - Linkage procedures performed by registry personnel using their available software and methods
- Linked records returned in deidentified format
  - Name and social security number removed, dates truncated to year only
  - Registry appended variables for primary tumor site code, histology code, year of diagnosis or age at diagnosis, and state of residence
- Cancer type determined using ICD-O-3 and grouped into major site categories



## Years of diagnoses available from state registries

State	starting year	ending year	total years
Arizona	1991	2006	15
Georgia	1991	2006	15
Michigan	1991	2006	15
Tennessee	1991	2006	15
Texas	1991	2006	15
California	1991	2005	14
Colorado	1991	2005	14
Connecticut	1991	2005	14
North Carolina	1991	2005	14
Virginia	1991	2005	14
Indiana	1991	2004	13
Iowa	1991	2004	13
Massachusetts	1991	2004	13
Wisconsin	1991	2004	13
Illinois	1991	2003	12
New York	1991	2003	12
Pennsylvania	1991	2003	12
Florida	1991	2002	11
Washington	1992	2003	11
Alabama	1996	2006	10
Kentucky	1994	2004	10
Oregon	1995	2005	10
Oklahoma	1996	2005	9
South Carolina	1996	2005	9
Ohio	1996	2003	7
New Jersey	1991	1999	8
Maryland	1991	1998	7



## Number of records to be analyzed from each state registry

State	Gulf	Non-gulf	Total
Alabama	261	394	655
Arizona	162	243	405
California	754	1174	1928
Colorado	154	399	553
Connecticut	38	148	186
Florida	444	768	1212
Georgia	476	781	1257
Illinois	165	274	439
Indiana	114	179	293
Iowa	73	170	243
Kentucky	123	205	328
Maryland	52	80	132
Massachusetts	62	180	242
Michigan	206	350	556
New Jersey	42	83	125
New York	213	424	637
North Carolina	588	692	1280
Ohio	158	244	402
Oklahoma	155	184	339
Oregon	81	152	233
Pennsylvania	210	370	580
South Carolina	254	386	640
Tennessee	374	432	806
Texas	971	1451	2422
Virginia	425	842	1267
Washington	234	465	699
Wisconsin	122	218	340



## Grouped cancer sites among Gulf and non-Gulf veterans

Primary Site	Gulf	Non-Gulf	Total
Oral Cavity and Pharynx	233	383	616
Esophagus	57	109	166
Stomach	112	144	256
Liver	41	71	112
Gallbladder-Pancreas	92	163	255
Other digestive system	713	1095	1808
Lung	510	818	1328
Other Respiratory system	87	131	218
Bones, Joints, Soft Tissue	153	198	351
Melanoma	660	1015	1675
Other skin	31	46	77
Breast	356	848	1204
Female Genital System	207	465	672
Prostate	1104	2163	3267
Testis	449	556	1005
Other Male Genital System	27	28	55
Bladder	215	340	555
Other Urinary System	227	405	632
Eye & Orbit	19	28	47
Brain	247	367	614
Other nervous system	64	101	165
Endocrine - Collapsed	265	384	649
Hodgkin Lymphoma	207	230	437
Non-Hodgkin Lymphoma and CLL	403	598	1001
Multiple Myeloma	71	110	181
Leukemias	170	244	414
Mesothelioma	9	16	25
Kaposi Sarcoma	32	67	99
Ill-defined & Unknown types	178	219	397
			<b>18281</b>



## Planned Statistical Analyses

- Crude proportional incidence ratio (PIR)
  - proportional incidence of a specific cancer among all cancers in Gulf group compared to proportional incidence of that specific cancer in non-Gulf group
  - comparing ground deployed (Army and Marine) Gulf veterans to non-ground (Air Force and Navy) Gulf veterans and also to non-Gulf veterans
- Logistic regression analyses to control for potential confounders
- Standardized incidence ratios (SIR) for cancers with significantly increased PIR
  - Expected numbers based on proportion of specific cancer in SEER



## Demographic Characteristics

Characteristic	All matches from state cancer registries		All veterans in sample used for matching	
	Gulf	Non-Gulf	Gulf	Non-Gulf
N	6,939	11,342	621,902	746,248
% White	70	74	68	70
% Black	22	19	23	22
% Hispanic	4	3	5	5
% Other	4	4	4	4
% Male	88	82	93	87
Age in 1991				
% <20	3	3	1	4
% 20-24	15	9	40	31
% 25-29	14	11	26	27
% 30-34	14	12	15	16
% 35-39	17	16	10	12
% 40-44	18	20	6	8
% 45-49	11	15	2	4
% 50-54	5	9	0.6	1
% 55-59	3	5	0.2	1
% 60+	0	1	0	0
Age at diagnosis				
% <20	0	0	n/a	n/a
% 20-24	2	1		
% 25-29	8	5		
% 30-34	14	10		
% 35-39	14	10		
% 40-44	14	12		
% 45-49	16	16		
% 50-54	15	18		
% 55-59	11	14		
% 60+	7	12		



## Conclusions

- This study will cover majority of population (according to data from 2000 census)
  - about 85% of the US adult population
  - about 83% of the Gulf and non-Gulf veteran population
- Study should answer questions regarding whether there are malignancies related to military service in the Gulf War
- Study methodology can be applied to future studies examining potential exposures and cancer outcomes

# Longitudinal Health Study of Gulf War Era Veterans

Han K. Kang, Dr.P.H.  
Director  
War-Related Illness and Injury Study Center  
and  
Environmental Epidemiology Service  
Department of Veterans Affairs  
Washington, DC

Meeting of the Research Advisory Committee  
on Gulf War Veterans' Illnesses

September 15-16, 2008

## Specific Aims

- To determine if the health status of Gulf War veterans is better, worse, or the same as Gulf Era veterans ten or more years after the war
- To characterize how the health status of Gulf War and Gulf Era veterans has changed since the National Health Survey which was completed 10 years ago

## Primary Hypotheses

Almost ten years after the war, Gulf War veterans will have an equal prevalence or mean level on the following health measures compared to Gulf Era veteran controls:

1. Cause-specific and overall mortality rates
2. Health care utilization
3. Chronic medical conditions
4. PTSD and other psychological conditions
5. General health perceptions and functional status

## Distribution of Gulf War Veterans and Gulf Era Veterans in the Survey by Gender and Unit Component

Unit Component	Gender		Total
	Male	Female	
Active	4,800	1,200	6,000
Reserve	4,000	1,000	5,000
National Guard	3,200	800	4,000
Total	12,000	3,000	15,000

Responses			
National Survey Response	Gulf	Gulf Era	Total
Yes	5469	3353	8822
No	642	506	1148
Total	6111	3859	9970

Response rate = 33.7%

## Possible Reasons for Low Response Rate

- Survey fatigue
- Signed informed consent requirement
- HIPAA requirement
- No direct benefits

## Selected Diagnoses for Gulf and Gulf Era Veterans Seen at a VA Healthcare Facility<sup>1</sup>

Diagnosis <sup>2</sup> ICD-9 Categories	Gulf (n=6,306)				Gulf Era (n=4,058)			
	Respondents (n=2,802)		Non-Respondents (n=3,504)		Respondents (n=1,395)		Non-Respondents (n=2,663)	
	n	%	n	%	n	%	n	%
Infectious and Parasitic Diseases (001-139)	573	20.4	729	20.8	197	14.1	452	17.0
Malignant Neoplasms (140-209)	114	4.1	132	3.8	58	4.2	98	3.7
Benign Neoplasms (210-239)	341	12.2	348	9.9	109	7.8	242	9.1
Diseases of Endocrine/Nutritional/Metabolic Systems (240-279)	1109	39.6	1078	30.8	401	28.7	778	29.2
Diseases of Blood and Blood Forming Organs (280-289)	195	7.0	220	6.3	71	5.1	153	5.7
Mental Disorders (290-319)	1185	42.3	1480	42.2	368	26.4	889	33.4
Diseases of Nervous System/Sense Organs (320-389)	1198	42.8	1325	37.8	516	37.0	979	36.8

1. Hospitalization and outpatient visits as of September 30, 2005.

2. Veterans can have multiple diagnoses with each healthcare encounter. However, a veteran is counted only once in any single Diagnostic Category but can be counted in multiple categories.

## Selected Diagnoses for Gulf and Gulf Era Veterans Seen at a VA Healthcare Facility<sup>1</sup>

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	n	%	n	%	n	%	n	%
Diseases of Circulatory System (390-459)	1007	35.9	1071	30.6	381	27.3	825	31.0
Diseases of Respiratory System (460-519)	1035	36.9	1181	33.7	407	29.2	774	29.1
Diseases of Digestive System (520-579)	1002	35.8	1211	34.6	380	27.2	883	33.2
Diseases of Genitourinary System (580-629)	695	24.8	777	22.2	277	19.9	549	20.6
Diseases of Skin (680-709)	779	27.8	902	25.7	241	17.3	560	21.0
Musculoskeletal System and Connective Tissues (710-739)	1421	50.7	1681	48.0	543	38.9	1185	44.5
Symptoms, Signs and Ill Defined Conditions (780-799)	1416	50.5	1719	49.1	541	38.8	1121	42.1
Injury /Poisonings (800-999)	702	25.1	915	26.1	268	19.2	637	23.9

1. Hospitalization and outpatient visits as of September 30, 2005.

2. Veterans can have multiple diagnoses with each healthcare encounter. However, a veteran is counted only once in any single Diagnostic Category but can be counted in multiple categories.



**Frequency and Estimated Prevalence Rate of Selected Self-reported Chronic Medical Conditions.**

Health Outcomes/Conditions	Gulf (n=6111)		Gulf Era (n=3859)		Adjusted RR (95% CI*)
	n	%	n	%	
Arthritis	2206	36.9	1231	32.4	1.20 (1.13-1.27)
Fibromyalgia	605	10.3	296	7.9	1.29 (1.12-1.48)
Skin cancer	713	12.0	447	11.8	1.09 (0.97-1.22)
Other cancer	621	10.4	369	9.7	1.09 (0.96-1.24)
Dermatitis or any other skin trouble	2027	34.0	920	24.2	1.41 (1.32-1.51)
Cirrhosis of the liver	502	8.4	240	6.3	1.30 (1.12-1.52)
Hepatitis	651	10.9	339	8.9	1.20 (1.06-1.37)
Chronic Fatigue Syndrome	1082	18.2	340	9.0	1.98 (1.76-2.23)

\* RR= risk ratio, CI = confidence interval. Adjusted for age, gender, race, body mass index, current cigarette smoking, rank, branch of service, and unit component (active duty, National Guard, or Reserve).

**(Continued) Frequency and Estimated Prevalence Rate of Selected Self-reported Chronic Medical Conditions.**

Health Outcomes/Conditions	Gulf (n=6111)		Gulf Era (n=3859)		Adjusted RR (95% CI*)
	n	%	n	%	
Gastritis	1643	27.4	685	18.1	1.52 (1.40-1.65)
Irritable bowel syndrome	1138	19.1	479	12.6	1.50 (1.35-1.66)
Diabetes	742	12.5	427	11.3	1.11 (0.99-1.25)
Other endocrine disorder	770	12.9	406	10.7	1.24 (1.11-1.39)
Repeated seizures	605	10.2	262	6.9	1.43 (1.24-1.66)
Depression	1866	31.1	777	20.4	1.50 (1.39-1.61)
Neuralgia or neuritis	797	13.4	368	9.7	1.39 (1.23-1.57)
Any disease of the genital organ	797	13.4	408	10.8	1.23 (1.08-1.39)
Coronary heart disease	671	11.3	355	9.4	1.22 (1.08-1.39)
Hypertension	1811	30.1	1074	28.2	1.11 (1.04-1.19)

\* RR= risk ratio, CI = confidence interval. Adjusted for age, gender, race, body mass index, current cigarette smoking, rank, branch of service, and unit component (active duty, National Guard, or Reserve).

## Frequency of Symptom-Based Conditions According to Deployment Status

Health Outcomes	Gulf n	%	Gulf Era n	%	Adjusted RR (95% CI)
CFS-Like Illness	574	9.4	132	3.4	2.38 (1.97-2.87)
Multisymptom Illness	2180	36.5	446	11.7	3.05 (2.77-3.36)

## 2005 Longitudinal Health Study

### Multisymptom Illness (MSI)

- Unexplained multisymptom illness is defined as having several different symptoms together that persist for 6 months or longer and are not adequately explained by conventional medical or psychiatric diagnoses.
- Unexplained multisymptom illness might include things like fatigue, muscle or joint pain, headaches, memory problems, digestive problems, respiratory problems, skin problems, or any other unexplained symptoms. These problems are often not labeled at all, but may sometimes be diagnosed as chronic fatigue syndrome, fibromyalgia, irritable bowel syndrome, or multiple chemical sensitivity.
- Since January 1991, have you ever experienced unexplained multisymptom illness that lasted 6 months or longer? Yes/No

## 2005 Longitudinal Health Study

### Chronic Fatigue Syndrome (CFS)-Like Illness

Revised definition based on variables in 2005 survey questionnaire:

In past 12 months, persistent problems with fatigue lasting > 24 hours after exertion and persistent problems with at least 3 of the following 7 symptoms: Headaches, sore throat, tender lymph nodes, muscle aches/cramps, joint aches/pain, awoken feeling tired or worn out after a full night of sleep, and difficulty concentrating/reasoning or memory loss.

AND

None of the following medical conditions:

Arthritis, skin cancer, any other cancer, cirrhosis of liver, hepatitis, diabetes, other endocrine disorder, repeated seizures/convulsions/blackouts, neuralgia/neuritis, disease of genital organs, coronary heart disease, stroke/cerebral vascular accident, tachycardia/rapid heart, asthma, emphysema/chronic bronchitis, and repeated bladder infections.

## Mental Health Related Outcomes Compared between Gulf and Gulf Era Veterans in 2005

Mental Health Outcomes	Gulf (n=6111)		Gulf Era (n=3859)		Adjusted RR(95%CI)
	n	%	n	%	
PTSD Checklist (PCL-C) (past 4 weeks)	928	15.2	176	4.6	2.98 (2.54-3.50)
Major Depressive Disorder (past 2 weeks)	908	14.9	224	5.8	2.34 (2.03-2.70)
Other Depressive Disorder (past 2 weeks)	397	6.5	152	4.0	1.55 (1.28-1.86)
Panic Disorder (past 4 weeks)	546	9.0	138	3.6	2.28 (1.89-2.74)
Generalized Anxiety Disorder (past 4 weeks)	675	11.1	142	3.7	2.67 (2.24-3.19)
Somatoform Disorder (past 4 weeks)	1385	22.7	349	9.1	2.37 (2.12-2.66)
Alcohol Abuse (past 6 months)	997	16.4	461	12.0	1.24 (1.11-1.37)
Taking med for anxiety/depression/stress	912	15.0	404	10.5	1.45 (1.30-1.63)

RR= risk ratio, CI = confidence interval. Adjusted for age, gender, race, body mass index, current cigarette smoking, rank, branch of service, and unit component (active duty, National Guard, or Reserve).

**SF-12 Scores and Standard Deviation**

Score	Gulf Veterans (n=6,111)	Gulf Era Veterans (n=3,859)	p-value <sup>a</sup>
Physical	46.9 (11.4)	50.1 (10.1)	<.0001
Mental	45.8 (12.4)	50.4 (10.2)	<.0001

<sup>a</sup> Probability value from 2-sample t-test.

**Percent Distribution of Perception of General Health Reported by Veterans\***

Health Status	Gulf Veterans (n=6,111)	Gulf Era Veterans (n=3,859)
Excellent	9.1	15.8
Very good	26.0	37.7
Good	39.0	34.0
Fair	20.6	10.6
Poor	5.3	2.0

\* p < 0.0001, p significance probability by chi-square test of independence between Gulf / Gulf Era deployment status.

## Summary

Response rate of 34% of living members of original panel of 30,000

Through September 20, 2005:

- 6,306 (41%) of Gulf veterans have received health care from VA
- 4,058 (28%) of Gulf Era veterans have received health care from VA

Indices which showed poorer health in 2005 among Gulf respondents compared with Gulf Era respondents

- Functional Impairment
- Limitation of activities
- Health care utilization due to illness: clinic visits and/or hospitalizations during previous 12 months

## Summary (continued)

- A wide range of medical and psychological conditions were self-reported as doctor diagnosed during lifetime
  - Most common conditions (listed in rank order): arthritis, dermatitis, depression, hypertension, gastritis, irritable bowel syndrome, and chronic fatigue syndrome
  - All were significantly associated with Gulf War deployment status
- Unexplained Multisymptom Illness and CFS-Like Illness (symptom-based medical conditions) were significantly associated with Gulf War deployment status
- SF-12: physical (PCS) and mental scales (MCS) had lower mean values among Gulf than Gulf Era veterans

## Other Current Research

- Examination of changes in health status during the past 10 years—comparison of veterans' responses to medical conditions in 2005 with the same questions answered during initial survey contact in 1995
- Review of medical records from providers as confirmation of self-report on survey questionnaires
- Comparison of mortality among 15,000 Gulf compared to 15,000 Gulf Era veterans



## **War Related Illness and Injury Study Center**

East Orange, New Jersey

Meeting of the Research Advisory Committee  
on Gulf War Veterans' Illnesses  
September 15 and 16, 2008  
Washington, DC

Presented by the VA NJ War Related Illness and Injury Study Center (WRIISC)

## **NJ Gulf War Research Center**

- In existence from 1999 – 2000
- GWV research focus on:
  - Immunologic function
  - Cardiovascular function
  - Cognitive function
  - Psychiatric function
  - Evaluation and longitudinal follow up of veterans with medically unexplained symptoms

Presented by the VA NJ War Related Illness and Injury Study Center (WRIISC)

## **WRIISC**

- In existence from 2001 – Present
- GWV research focus on:
  - Health services outcomes research
  - Behavioral interventions
    - Dr. Quigley:
      - Heart Rate Variability Biofeedback as a Possible Treatment for Gulf War Illness
    - Dr. Chandler:
      - Telemedicine Intervention for Veterans with Gulf War Illness

Presented by the VA NJ War Related Illness and Injury Study Center (WRIISC)



## **Heart Rate Variability Biofeedback as a Possible Treatment for Gulf War Illness**

Presented by the VA NJ War Related Illness and Injury Study Center (WRIISC)



- Biofeedback is the measurement and display of information to a person about their on-going physiology used to help them attain some control over their physiology.
- Autonomic nervous system dysregulation is presumed to occur in many disorders and reduction in this dysregulation is presumed to have a salutary effect on physical symptoms.

Presented by the VA NJ War Related Illness and Injury Study Center (WRIISC)

## **Uses of Biofeedback**

- Clinical uses of biofeedback include:
  - Decreased blood pressure in hypertension
  - Decreased airway restriction in asthma
  - Decreased A1c in diabetes
  - Decreased headache pain
  - Decreased symptoms in many disorders including depression, fibromyalgia, chronic back pain, chronic myofascial pain, temporomandibular pain, etc.

Presented by the VA NJ War Related Illness and Injury Study Center (WRIISC)

## What is Heart Rate Variability?

- Heart rate variability is variation in heart rate due to respiratory and other regulatory rhythms in the body
- A prominent frequency component in the HRV is the High Frequency HRV (about 0.15-0.4 Hz or 9-24 breaths per minute)
- Slowing the breathing rate to 4.5-7 breaths per minute moves the HRV peak to a lower frequency range (0.075-0.12 Hz)

Presented by the VA NJ War Related Illness and Injury Study Center (WRIISC)

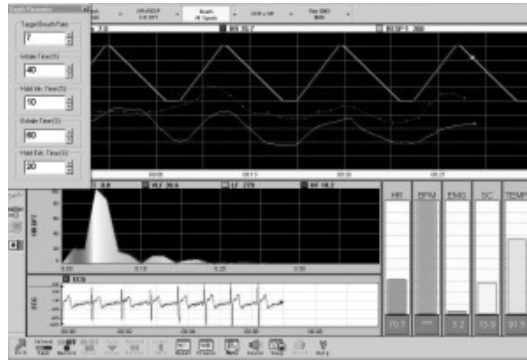
## HRV Biofeedback

- HRV biofeedback is training of this slower breathing rate with attention to the “best” breathing frequency for each individual
- Individuals have a particular resonance frequency somewhere between 4.5-7 breaths per minute that is determined in part by the person’s height

Presented by the VA NJ War Related Illness and Injury Study Center (WRIISC)

## HRV Biofeedback (cont.)

HRV biofeedback training begins with the determination of the resonant frequency for the individual using a pacing stimulus



Presented by the VA NJ War Related Illness and Injury Study Center (WRIISC)

## How does HRV BF change Physiology?

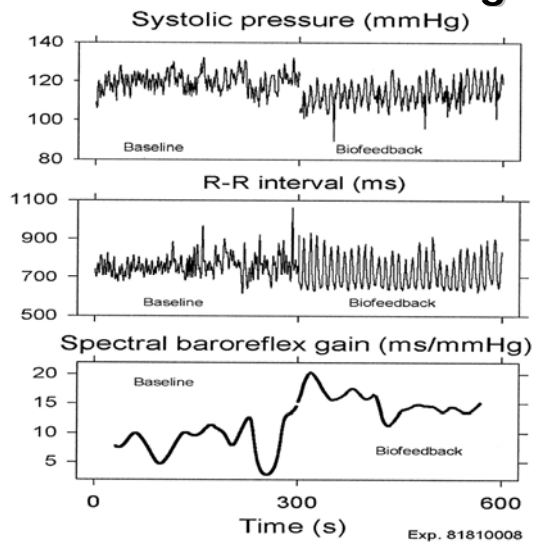


Fig. 1. Recording from one participant before and during biofeedback. In this participant, biofeedback increased systolic pressure and R-R interval oscillations, decreased mean systolic pressure, and increased baroreflex gain.

Lehrer et al., 2003

Presented by the VA NJ War Related Illness and Injury Study Center (WRIISC)

## Proposed Study

- In collaboration with Dr. Paul Lehrer of Robert Wood Johnson Medical School
- Rationale: HRV biofeedback was shown in a small scale study to improve function, reduce pain and reduce depression at 3 month follow-up in patients with fibromyalgia. Another small study showed reductions in health care costs in patients with IBS, FM, myofascial pain, etc. who were given HRV BF in a primary care setting (in a completer analysis).

Presented by the VA NJ War Related Illness and Injury Study Center (WRIISC)

## Study Aim & Methods

- To test the effects of a 10 session HRV biofeedback treatment in veterans with Gulf War Illness compared to a placebo control condition
- The primary outcome measure was the Clinical Global Impression Scale score.
- Secondary outcomes included depression and physiological changes in response to diesel vapor challenge task both pre- and post-treatment

Presented by the VA NJ War Related Illness and Injury Study Center (WRIISC)



- Expect decreased CGI scores and to diesel vapor challenge task, reduced hyperventilation and increased HRV.

Presented by the VA NJ War Related Illness and Injury Study Center (WRIISC)



## Telemedicine Intervention for Veterans with Gulf War Illness: Preliminary Analyses

Helena K. Chandler

Donald S. Ciccone

VA NJ WRIISC

Department of Psychiatry, UMDNJ-New Jersey Medical School

This material is the result of work supported by an HSR&D Grant (GWI-04-355) to Dr. Ciccone as well as resources and the use of facilities at the War Related Illness and Injury Center (WRIISC) and the East Orange, New Jersey Veterans Affairs Medical Center

Presented by the VA NJ War Related Illness and Injury Study Center (WRIISC)

## Study Aims

- Determine the clinical efficacy of a brief, remotely-delivered symptom management intervention for veterans with multiple physical symptoms
- Develop and test models of change in symptom severity, physical functioning, and healthcare use in veterans with multiple physical symptoms

Presented by the VA NJ War Related Illness and Injury Study Center (WRIISC)

## Rationale

- Physical symptoms predict physical functioning, work-related disability and health care use
- Psychiatric morbidity is often associated with physical symptom severity
- Prior studies suggest CBT may be able to improve physical functioning and other outcomes associated with multiple physical symptoms

Presented by the VA NJ War Related Illness and Injury Study Center (WRIISC)

## Method

- Eligibility criteria:
  - $\geq 80^{\text{th}}$  percentile of ambulatory care visits
  - Gulf War Illness (Fukuda/CDC case criteria)
  - Random group assignment
  - Face-to-face treatment, Telephone treatment, Waitlist control
- CBT Treatment: 10 sessions over 12 weeks
- Assessment schedule:
  - T1: Enrollment T2: 3 months T3: 12 months

Presented by the VA NJ War Related Illness and Injury Study Center (WRIISC)

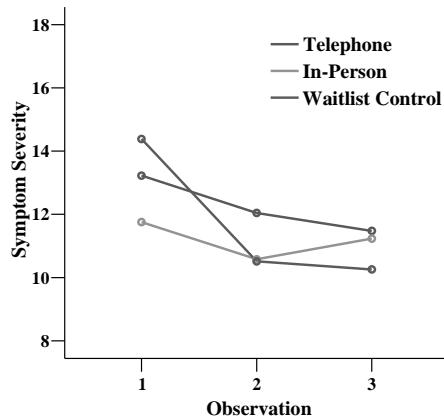
## Sample Characteristics

	Telephone (N=42)	In-Person (N=43)	Waitlist (N=43)
% Male	95.2% (40)	93.0% (40)	95.3% (41)
Mean age	57.6 (6.6)	55.4 (8.2)	56.8 (7.3)
% White	48.7% (19)	42.9% (18)	42.9% (18)
% Married	48.8% (20)	46.5% (20)	38.1% (16)
% Education >HS	45.2% (19)	44.2% (19)	55.8% (24)
<i>Employment</i>			
% Working (F/T, P/T)	26.8% (11)	20.9% (9)	26.2% (11)
% Unable to work	46.3% (19)	58.1% (25)	52.4% (22)
% Retired	14.6% (6)	11.6% (5)	14.3% (6)
% Unemployed	12.2% (5)	9.3% (4)	7.1% (3)
<i>Percent VA Disability</i>			
Mean (SD)	54.2 (32.7)	48.3 (34.5)	54.8 (30.1)

p>.10 for all group comparisons

Presented by the VA NJ War Related Illness and Injury Study Center (WRIISC)

## Effect of Treatment on Symptom Severity (Intent to Treat)

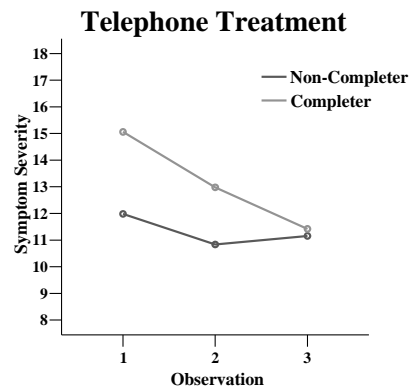
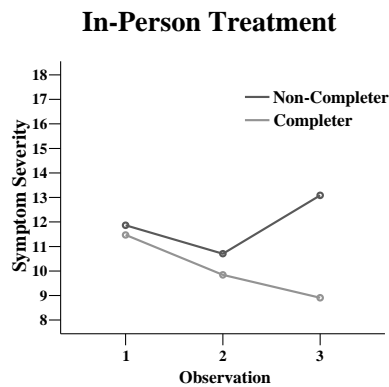


Symptom severity improved over time ( $F=6.7, p<.005$ )

Veterans in the control group improved more than the treatment groups ( $F=3.88, p<.05$ )

Presented by the VA NJ War Related Illness and Injury Study Center (WRIISC)

## Comparison of Completers vs. Non-Completers on Symptom Severity

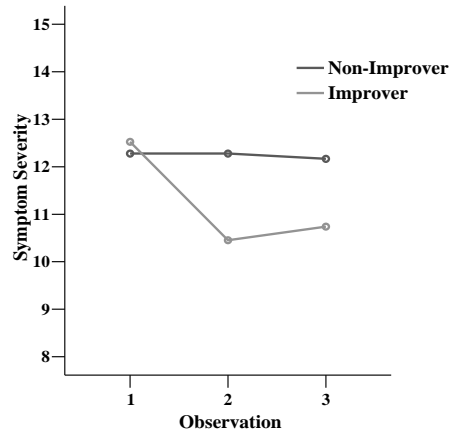


Veterans who completed 10 sessions showed greater reductions in symptom severity over time ( $F=8.3, p<.005$ )

Presented by the VA NJ War Related Illness and Injury Study Center (WRIISC)



## Effect of Reduced Catastrophizing on Symptom Severity



Reductions in catastrophic thinking over 12 months are associated with reduced symptom severity ( $F=5.99, p<.05$ )

Presented by the VA NJ War Related Illness and Injury Study Center (WRIISC)

## Conclusions

- Brief CBT intervention was not associated with a reduction in physical symptoms
- Veterans with multiple physical symptoms experience fewer symptoms over time
- Changes in catastrophizing appear to be associated with reduction in physical symptoms

Presented by the VA NJ War Related Illness and Injury Study Center (WRIISC)

## Next Steps

- Does treatment effect daily behavioral outcomes such as functioning or health care utilization?
- Is there a remission in GWI over time?
- Is the advantage of treatment completion due to selection bias (ie to an artifact)?
- What effect does change in other coping strategies have on physical symptoms?

Presented by the VA NJ War Related Illness and Injury Study Center (WRIISC)

# **Update on Research in Persian Gulf War Veterans Illnesses**

**September 2008**

**Beatrice Alexandra Golomb, MD, PhD**

## **RECAP**

### **Epidemiology**

- **GWV Hospitalization Study**

### **Relation to Similar Conditions:**

- **CFS compared in GWV vs civilians**

### **Findings on Similar Conditions**

- **FM pts show ↓ NAA:cr in Hippocampal**

### **Exposure Relations: Animal Studies**

- **Sarin exposed rats show (additional) delayed pathology**

### **Human Findings Relevant to Exposures**

- **NTE (neuropathy target esterase) relates to (some) motor neuron disease**

## I. Fate of III GWV -- Hospitalizations

### **GWV Long-Term Hospitalization Experience**

**Finding:** No significant association long term hospitalizations and war-related exposures

**Design:** Prospective longitudinal study of GWV

**Ss:** 211,642 GWV still on active duty as of 10-1-94 They were assessed for attrition at 3 yr intervals over 10yr f/u

**Goal:**

1. Compare active duty to separated
2. Assess probability of hospitalization if stay active duty
3. Assess predictors of hospitalization if stay active duty

Hooper 2008 The long-term hospitalization experience following military service in the 1991 Gulf War among veterans remaining on active duty 1994-2004. BMC Public Health 8:60.

## Hospitalization Study

**Outcome:** All-cause hospitalizations

**Predictors:** Demographic, military service characteristics, “GW exposure variables”, hospitalizations data

**GW Exposures** Included:

- **Anthrax &/or BT vaccine** (*not stated how assessed*)
- **Pot’I N Aqt Exposure:** Khamisiyah 3-level exposure (not at risk, at risk not exposed, exposed) (from NHRC & CHPPM)
- **Oil Fire Smoke** (from NHRC & CHPPM)
- **Presence in Theater** during ground combat

**Analysis:** Cox proportional hazards

Hooper 2008 The long-term hospitalization experience following military service in the 1991 Gulf War among veterans remaining on active duty 1994-2004. BMC Public Health 8:60.

## Hospitalization Study

**Results:** 43,456 hospitalized at least 1ce (16.4%)

- a. Active vs separated: ↑ officer, older, married
- b. Top Hospitalization Diagnoses:

1. Musculoskeletal
2. Injury and poisoning
3. Digestive disorders
4. Signs Symptoms and Ill Defined

Also = top dx in 4800 in-theater hospitalizations: 2,3,4,1

- c. “Selected war-related exposures or experiences did not appear to influence separation with exception of in-theater presence during ground war”

Hooper 2008 The long-term hospitalization experience following military service in the 1991 Gulf War among veterans remaining on active duty 1994-2004. BMC Public Health 8:60.

## **Hospitalization Study**

- 4. Some diagnoses ↑ progressively over time:**
- **Signs symptoms and ill-defined conditions**
  - **Cardiovascular conditions**
  - **Endocrine and metabolic**
  - **Mental disorders**

**Hooper 2008 The long-term hospitalization experience following military service in the 1991 Gulf War among veterans remaining on active duty 1994-2004. BMC Public Health 8:60.**

## **Hospitalization Study**

### **CONCLUSION:**

**No significant association long term hospitalizations and war-related exposures**

### **BUT:**

**Hooper 2008 The long-term hospitalization experience following military service in the 1991 Gulf War among veterans remaining on active duty 1994-2004. BMC Public Health 8:60.**

## Hospitalization Study

### LIMITATIONS:

- No comparison group: Can't tell if hospitalizations are ↑ (all or specific)
- Focuses on those who remained on active duty: signif health problems may lead to separation from military

Hooper 2008 The long-term hospitalization experience following military service in the 1991 Gulf War among veterans remaining on active duty 1994-2004. BMC Public Health 8:60.

## Hospitalization Study

### LIMITATIONS:

Misclassification bias: Expected bias to the null

Ax Vax: Listed rate 0.4% all groups. ~ 21% of GWV got Ax, not 0.4%.  
If used DoD records, most vaccinated will be listed in unvaccinated group)

N agt: Use plume modeling, many minimally exposed; Possible nonKhamisiyah N agt episodes not included.

Omitted variable bias. E.g. Did not include key exposures:

- o PB
- o Pesticides

If the bad exposures are in the "unexposed" groups will miss true relationships

Hooper 2008 The long-term hospitalization experience following military service in the 1991 Gulf War among veterans remaining on active duty 1994-2004. BMC Public Health 8:60.

## II. Comparison to Similar Groups: CSF in GWV vs Civilian (male)

### **2. Chronic Fatigue Synd in Male GWV**

**Goal:** Compare CFS in GWV vs. civilians

**Subjects:**

- 45 male veterans from the GW Research Center;
- 84 male civilians fm the CFS Cooperative Center

New fatigue producing substantial impairment in phys fxning, lasting  
≥6 mo;

≥4 of: sore throat; tender LN as w/ infection; myalgia; arthralgia; new  
HA; unrefreshing sleep; attention/ concentration problems; much  
worse w/ min exertion

**Exclusions:** ID'd medical causes of fatigue; psychiatric exclusions for  
CFS (e.g. substance/alcohol in last 2yr..)

Cicccone 2008. Chronic Fatigue Syndrome in Male Gulf War veterans and Civilians: A further  
test of the single syndrome hypothesis. J Health Psychology 13: 529-536



## Chronic Fatigue Synd in Male GWV

**Assessments:**

**MCS:** exposure to >1 odorant produces sx in >1 body system plus efforts to avoid those odorants

**FM:** Am Coll Rheumatol Clin Criteria

**Major Psych Illness:** By DIS (structured interview). Depression, PTSD, generalized anxiety, Axis I Dx.

**SF-36** (QOL scale): phys fxn, phys disabil, pain, fatigue (vitality), gen health, soc fxn, emotl disabil, mental health index

Days in bed/ month; Days “cut down” (w/ ↓ activity) / mo

Disability status

Ciccone 2008. Chronic Fatigue Syndrome in Male Gulf War veterans and Civilians: A further test of the single syndrome hypothesis. J Health Psychology 13: 529-536

## Chronic Fatigue Synd in Male GWV

<b><u>Results:</u></b>	<b>Black GWV N=12</b>	<b>White GWV N=30</b>	<b>White Civilians N=82</b>	<b>2 vs 3  P</b>
<b>Gradual onset</b>	<b>93%</b>	<b>90%</b>	<b>57%</b>	<b>&lt; 0.01</b>
<b>Sudden flu-like</b>	<b>7%</b>	<b>10%</b>	<b>43%</b>	<b>&lt; 0.01</b>
<b>Fibromyalgia</b>	<b>7%</b>	<b>0%</b>	<b>22%</b>	<b>&lt; 0.01</b>
<b>MCS</b>	<b>27%</b>	<b>27%</b>	<b>27%</b>	<b>NS</b>
<b>Depression</b>	<b>80%</b>	<b>37%</b>	<b>52%</b>	<b>NS</b>
<b>PTSD</b>	<b>47%</b>	<b>27%</b>	<b>3%</b>	<b>&lt; 0.01</b>
<b>Psych axis 1 dx</b>	<b>93%</b>	<b>70%</b>	<b>61%</b>	<b>NS</b>

Ciccone 2008. J Health Psychology 13: 529-536

## Chronic Fatigue Synd in Male GWV

<u>Results:</u>	Black GWV N=12		White GWV N=30	White Civilians N=82	2 vs 3  P
Phys disability	11		21	7	< 0.05
Days cutdown/mo	7		7	14	< 0.05
Days abed/ mo	3		3	4	NS
SF36 Fatigue	21		21	14	NS
Emot'l Disabil	29		44	54	NS
Disability	?		13	43	< 0.01

Ciccone 2008. Chronic Fatigue Syndrome in Male Gulf War veterans and Civilians:  
 A further test of the single syndrome hypothesis. J Health Psychology 13: 529-536

## Chronic Fatigue Synd in Male GWV

GW Exposure Assessments: 9 exposures

64% reported exposure to 6 or more potentially toxic exposures on a "standard" list of 9 exposures: give as examples:

Oil fire smoke

Pesticides

Debris from scuds

Ciccone 2008. Chronic Fatigue Syndrome in Male Gulf War veterans and Civilians:  
 A further test of the single syndrome hypothesis. J Health Psychology 13: 529-536

## **Chronic Fatigue Synd in Male GWV**

### **Conclusion:**

**“Contrary to the single syndrome hypothesis, our results show that veterans and civilians differed on a broad range of illness characteristics” esp mode of onset (% rapid) and comorbid illness..**

**~all veterans gradual onset vs ~1/2 civilians**

**These findings “raises the possibility that CFS subgroups may have different underlying causes” – e.g. infection in civilians and !war related stress in GWV!**

**Ciccone 2008. Chronic Fatigue Syndrome in Male Gulf War veterans and Civilians: A further test of the single syndrome hypothesis. J Health Psychology 13: 529-536**

## **Chronic Fatigue Synd in Male GWV**

### **Limitations:**

**Small samples ?representativeness**

**Restricts to care-seeking individuals**

**Differences in SES (civilians higher educated)**

**Unexpected diffs AA vs caucasian leading to split in GWV group and smaller Ns**

**Multiple comparisons**

**Inference re: stress unfounded**

**Ciccone 2008. Chronic Fatigue Syndrome in Male Gulf War veterans and Civilians: A further test of the single syndrome hypothesis. J Health Psychology 13: 529-536**

## Rats Exposed to Sarin

**Ss:** Rats (freely moving)

**Exposure:** 1 time whole body sarin vapor:  $34.2 \pm 0.8 \mu\text{g/l}$  x 10min

- 35% died in 24h
- Toxic signs in rest from none to mod to severe (prolonged seizures)

**Outcomes:**

- Clinical signs
- Behavioral eval: Working field (activity); water maze (memory). Times: 6 wk, 4 mo, 6 mo.
- Histology (1wk, 1 mo, 6 mo)

Cell loss

Neuronal inflammation: PGE2

Glial activation: PBR (peripheral benzo receptors)

Grauer 2008. Single whole-body exposure to sarin vapor in rats: Long-term neuronal and behavioral deficits. *Toxicol Applied Pharmacol* 227: 265-74

### III. Information about Similar Groups: FM Biomarkers

(Dr. Clauw to review his...)

## **Fibromyalgia (FM) & HC Abnormalities**

**Goal:** assess FM vs control females' HC (hippocampus)  
with proton MRS (magnetic resonance spectroscopy)

**Design:** Case control

**Ss:** 16 female FM patients vs 8 "age and gender matched"  
healthy controls

**Outcomes:**

**NAA/Cr on proton MRS**

**Score on Fibromyalgia Impact Questionnaire**

Wood 2008 Hippocampal metabolite abnormalities in fibromyalgia. *J Pain* epubdate 2008/09/06.

## **Fibromyalgia (FM) & HC Abnormalities**

**Result:**

**1. Lower NAA/Cr in FM than controls:**

**NAA/Cr case: 1.20 +/- 0.13**

**NAA/Cr control: 1.34 +/- 0.10      P = 0.03**

**2. Lower NAA/Cr correlates with worse FM (higher score)**

**Spearman rank correlation: -0.681, P = 0.018**

**Limitations:**

**FM. Representativeness of samples. Females only.**

**NonGWV. Small sample: especially, few controls.**

Wood 2008 Hippocampal metabolite abnormalities in fibromyalgia. *J Pain* epubdate 2008/09/06.

## IV. Exposure Effects – Animal Studies

### Rats Exposed to Sarin

**Result:**

**Cell loss:** “typical” cell loss at 1 week

**Neuronal inflammation** (by PGE2)

Early ↑ : 20x incr PGE2 at 24hr that ↓ to 6 days.

Delayed ↑ : detected at 1 mo & cont'd to ↑ to 6mo

**Glial activation** (by PBR): follows neuronal damage:

Inc at 4 & 6mo after exposure

**Behavior:**

**Open field activity:** ↑activity, w/ no habituation over days

**Working memory paradigm** (water maze): Impaired working and reference memory with no improvement over time

Grauer 2008. Single whole-body exposure to sarin vapor in rats: Long-term neuronal and behavioral deficits. *Toxicol Applied Pharmacol* 227: 265-74

## Rats Exposed to Sarin

### Conclusion:

“Our data suggest long lasting impairment of brain functions in surviving rats following a single sarin exposure. Animals that seem to fully recover from the exposure, and even animals that initially show no toxicity signs, developed some adverse neural changes with time”

### Limitations:

- Relatively high dose
- 1-time exposure
- Limited spectrum of outcomes
- Rats

Grauer 2008. Single whole-body exposure to sarin vapor in rats: Long-term neuronal and behavioral deficits. *Toxicol Applied Pharmacol* 227: 265-74

## V. Exposure Relations to Health – Human Studies

## People Exposed to OPs: NTE & NMS

**Background:** (Tangential – can skip based on time)

The possibility that OPs contribute to MND is supported by the assoc of PON mutations to ALS; & (separately) by occurrence of MND in ppl with OPIDN – in which the enzyme NTE is inhibited by OPs

NTE is a neuron mb protein that is inhibited by OPs which also lead to development of OP-NTE neurotoxic complexes (“aged NTE”)

**Goal:** To see if there is an association of NTE to MNDs

**Ss:** A consanguineous kindred (Ashkenazi Jewish ancestry) and a genetically unrelated nonconsanguineous kindred (northern European) in which affected subjects develop progressive LE spastic weakness and wasting of distal upper and lower extremity muscles. Affected Ss resemble OPIDN & Troyer synd.

(Troyer syndrome involves distal muscle wasting + vbl cognitive)

Rainier 2008 Neuropathy Target Esterase Gene Mutations Cause Motor Neuron Disease *Am J Hum Genetics* 82: 780-785

## People Exposed to OPs: NTE & NMS

**Genome-wide linkage analysis:**

6 of 400 polymorphic microsatellite markers 10cM apart were homozygous for all affected in the consanguineous family.

Only markers adjacent to D19S209 (c’some 19) yielded an extended linked haplotype, spanning 22cM btn D19S565 and D19S884

In the smaller nonconsanguineous family the same markers also results in haplotype sharing in affected Ss c/w genetic linkage of this region.

Then used programs, GeneHunter, SimWalk2 to perform multipoint analyses : all methods gave maximum LOD score near marker D19S869. GeneHunter:  $P = 0.002$ ; SimWalk:  $p = 0.0004$

Rainier 2008 Neuropathy Target Esterase Gene Mutations Cause Motor Neuron Disease. *Am J Hum Genetics* 82: 780-785



## People Exposed to OPs: NTE & NMS

**Result:** Family 1: Each affected family member was homozygous for, & each obligate carrier heterozygous for a mutation in NTE\*

The mutation was absent in 105 control subjects.

This mutation disrupts an interspecies conserved residue w/in NTEs catalytic domain.

Family 2: affected family members were compound heterozygotes for two NTE mutations, also in NTEs catalytic domain\*\*

\*Substitution of guanine for adenine at NTE cDNA 3034 – causing subst'n of valine for methionine at amino acid position 1012.)

\*\*One involved a 4 base insertion that caused a frameshift & protein truncation p residue 1019 leading to missing last 235 residues of NTEs catalytic domain (extending from aa position 727 to 1216).

**Major Limitation:** Tangential to conditions reported in most GWV.

Rainier 2008 Neuropathy Target Esterase Gene Mutations Cause Motor Neuron Disease. *Am J Hum Genetics* 82: 780-785

## Questions?

## VI. Reply to Blazer Letter

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RAC Statement - September 14, 2008

Mr Chairman and members of the committee, thank you for the opportunity to speak. My name is Jim Bunker, and I am here as President of the National Gulf War Resource Center. We support the need to find biological markers of Gulf War Illness and related multi-symptom chronic illnesses, and to develop effective treatment, with priority on treating cognitive dysfunction.

We would like to see more information released to the public, such as working together to improve the Gulf War Veteran Information System reports in the future, to include data on Gulf War veterans in the VA system that were diagnosed with illnesses which may be either related to, or secondary to, undiagnosed multi-symptom illness.

We are grateful to the Research Advisory Committee for its commitment and hard work in developing treatment for cognitive dysfunction, and we would like to know whatever we can do to help, as one of the original advocacy organizations for these veterans.

Cognitive dysfunction is the single greatest barrier to our veterans' ability to maintain a productive, rewarding career and family life. One example among the thousands affected by undiagnosed multi-symptom illness is my own experience.

I started having problems while serving in Iraq. This began with sudden onset of labored breathing and muscle twitches, which advanced into muscle cramps. About five hours from onset, I was found in a fetal position on ground. While alert and able to hear what was going on around him, I could not respond at all. First responders gave me atropine; then they got medics who took me to our battalion aid station. After awhile, I was given another shot; whatever it was, it hurt. From there I was moved to the division aid station, the nearest army field hospital, and finally to the 410<sup>th</sup> Evac Hospital in Saudi Arabia. The staff there identified neurological problems in my left arm and right leg, which I still have to this day.

As time went on, I found it harder and harder to concentrate and do things such as reading, writing, and paying close attention. Sometimes I fogs out. Dr. Lea Steele recognized an instance when this was happening to me by the changes in my facial expression. One drug prescribed by the VA, Divalproex, helps somewhat, but not completely. If I work hard at doing something, then I am totally wiped out starting sometime between 11 am and 2 pm. The only way to recover is to lie down and rest for 4 hours. Thank you for all the work you are doing for all of us affected by this Illness. The Resource Center looks forward to continuing to advocate for your efforts.

*The NGWRC provides education and support to benefit Veterans, current active duty personnel, reservists, National Guard members, and their families who have served from 1990 to the present day.*

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RAC Statement - December 21, 2008

This is my statement made on 16 September 2008.

Mr Chairman and members of the committee, thank you for the opportunity to speak. My name is Jim Bunker, and I am here as President of the National Gulf War Resource Center. We support the need to find biological markers of Gulf War Illness and related multi-symptom chronic illnesses, and to develop effective treatment. After hearing from the speakers and reading the handouts given while here, I feel that a standard pool of veterans is needed for any and all work done in any research looking at the cause to and any other illnesses that might be related to the field of gulf war illness.

We feel that any research needs to use veterans as fellow:

1. Those entering the gulf from 1 August 1990 to 31 July 1991, these will be mostly the veterans that did the fighting in the war.
2. Those in the from 1 August 1991 to 31 December 1992 as these are veterans that did the clean-up after the war and as such was still exposed to many of the same things was us.
3. Veterans that was the gulf from 1 January 1996 to just before OIF.
4. Veterans of the first year of OIF.
5. Those in the service during 1991 and not deployed.

One thing that is going on is veterans that went in after 31 July 1991 and comes down with ALS can not get ALS due to service their service in the gulf. As it is now, the VA is only covering the veterans that the research did and that is from 1 August to 31 July 1991.

We are grateful to the Research Advisory Committee for its commitment and hard work in all that it has done over the years to help those of us sick from our time in the war, and we would like to know whatever we can do to help, as one of the original advocacy organizations for these veterans.

Thank you for all the work you are doing for all of us affected by this Illness. The Resource Center looks forward to continuing to advocate for your efforts.