Research Advisory Committee on Gulf War Veterans' Illnesses

October 27-28, 2003 Committee Meeting Minutes

U.S. Department of Veterans Affairs
811 Vermont Ave, Room 819
Washington, D.C.

DEPARTMENT of VETERANS AFFAIRS

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

I hereby certify the following minutes as being an accurate record of what transpired at the October 27-28, 2003, 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
Nicola Cherry
Beatrice Golomb
Joel Graves
Robert W. Haley
Marguerite Knox
William J. Meggs
Pierre J. Pellier
Steve Robinson
Steve Smithson
Lea Steele

Consultant to the Committee
Jack Melling

Guest Speakers
Maria Araneta
Betty Mekdeci
Han Kang
Carrolee Barlow
Wilkie Wilson
Nelda Wray
Hermona Soreq
Steven Berkowitz
Michael Kilpatrick
Robert Sheridan
Eugene Oddone
Susan Perez
Denise Hynes
Clare Mahan

Meeting Agenda

Monday, October 27, 2003

8:30 – 8:45	**Welcome, introductions, and opening remarks**	Mr. Jim Binns
8:45 – 9:30	**Birth Defects and Pregnancy Outcomes Following Service in the Gulf War** *Dr. Araneta, Assistant Professor at the University of California at San Diego, will present information from her studies on birth defects in children of Gulf War veterans. Her presentation will include the first release of the results from her study "Conception and Pregnancy During the Persian Gulf War: The Risk to Women Veterans" to be published in the November, 2003, issue of Annals of Epidemiology.*	Dr. Happy Araneta
9:30 – 10:15	**Information From a Registry of Birth Defects in Children of Gulf War Veterans** *Ms. Mekdeci is Executive Director of Birth Defects Research for Children, a non-profit organization that maintains a registry of children of Gulf War veterans with birth defects. She will present data from the registry, as well as preliminary information from a cooperative study of Goldenhar Syndrome in children of Gulf War veterans.*	Ms. Betty Mekdeci
10:15 – 10:30	***Break***	
10:30 – 11:15	**Findings on Birth Defects from the National Survey of Gulf War Veterans** *Dr. Kang is Director of VA's Environmental Epidemiology Program and the War-Related Injury and Illness Study Center in Washington, D.C. He will present new results on birth defects from VA's National Survey of Gulf War Veterans, including medical record corroboration of birth defects reported by Gulf Veterans.*	Dr. Han Kang
11:15-11:45	**Discussion**	
11:45-12:00	**Update on Published Research**	Dr. Lea Steele
12:00-1:00	***Lunch***	

1:00 – 1:45	**NTE and Identification of Possible Molecular Targets of Neurotoxic Exposures in Gulf War Veterans** *Dr. Barlow, currently with Merck Research Laboratories, will present work conducted with colleagues at Salk Institute that demonstrated the effects of organophosphate pesticides on neuropathy target esterase (NTE), including the role of NTE genetic variability. This research may have profound implications for our understanding of the effects of these chemicals on humans. Dr. Barlow will outline the potential for genomic research to identify targets for treatments of potential benefit to both ill Gulf War veterans and others at risk of future terrorist or military chemical attack.*	Dr. Carrolee Barlow
1:45 – 2:30	**Neurotoxins and Gulf War Illness: An Overview of VA's Research Enhancement Award Program (REAP)** *Dr. Wilson, VA Senior Research Career Scientist and Professor of Pharmacology at Duke University, will describe the work of VA's Neurotoxins and Gulf War Illness Program, which will examine proteins expressed in patient and animal samples following exposure to neurotoxins. This research has the potential to identify biomarkers that identify exposed individuals, as well as molecular targets for treatment interventions.*	Dr. Wilkie Wilson
2:30-2:45	***Break***	
2:45 – 4:30	**Update on VA Gulf War Illness Research Programs** *Dr. Wray is VA's Chief Research and Development Officer, and will update the committee on recently funded deployment health studies. She will also present information on plans for VA's Neuroimaging Resource Center and the Gulf War illness pilot project from the San Francisco VA.*	Dr. Nelda Wray
	VA Study of AChE-R in Gulf War Veterans *Dr. Soreq, of Hebrew University in Jerusalem, and Dr. Concato, Chief of Epidemiology at the West Haven VA, will present initial results of a VA study to determine whether ill Gulf War veterans have high levels of a mutant form of the enzyme acetycholinesterase (AChE-R), shown in previous studies to be associated with exposures to AChE-inhibiting chemicals such as those encountered during the Gulf War. Dr. Soreq's laboratory has developed a novel treatment that may be effective in treating this abnormality.*	Dr. Hermona Soreq Dr. John Concato
4:30-5:00	**Public Comment**	
5:00	***Adjourn for the day***	

Tuesday, October 28, 2003

8:30 – 9:45	**Department of Defense Research on Gulf War Veterans' Illnesses and Chemical Defense** *Dr. Kilpatrick will present information on DOD's research on Gulf War illnesses and deployment health, and an overview of DOD research relating to medical chemical defense.*	Dr. Michael Kilpatrick
9:45 – 10:30	**Additional Findings from the VA ALS Study and Update on the ALS Registry** *Dr. Oddone, Director of the Health Services Research Center at Duke University, and Principle Investigator of VA's study of ALS in Gulf War Veterans, will present more detailed results of analyses from that study, and will update the committee on VA's ALS Registry.*	Dr. Eugene Oddone
10:30-10:45	***Break***	
10:45 – 11:15	**Monitoring the Health of Gulf War Veterans Using Existing VBA Data Systems** *Ms. Perez is Assistant Director for Data and Information Services at the Office of Performance Analysis and Integrity at VA's Veterans Benefits Administration. She will present information on benefits claims data resources and how they might be used to monitor the health of Gulf War veterans.*	Ms. Susan Perez
11:15 – 11:45	**Monitoring the Health of Gulf War Veterans Using VHA Data and Information Resources** *Dr. Hynes directs the VA Information Resource Center, and will present information on the databases and resources available at VA's Veterans Health Administration, and how they might be used to monitor Gulf veterans' health and clinical care.*	Dr. Denise Hynes
11:45 – 12:15	**Q&A, Discussion**	
12:15 – 1:15	***Lunch***	

1:15 – 1:45	**Anthrax Vaccinations and Health Outcomes in the National Survey of Gulf War Veterans** *Dr. Kang will present results from VA's National Survey of Gulf War veterans on a subgroup of veterans known to have received the anthrax vaccine in association with Gulf War deployment.*	Dr. Han Kang
1:45 – 2:00	**Federal Trials of the Anthrax Vaccine**	Dr. Jack Melling
2:00 – 3:30	**Committee Business**	Mr. Jim Binns
3:30 – 4:00	**Public Comment**	
4:00	***Adjourn***	

Welcome, introductions, opening remarks

Mr. James H. Binns, Jr., Chairman

Chairman James Binns called the meeting to order at 8:30 a.m. He welcomed the participants and attendees.

Birth Defects and Pregnancy Outcomes Following Service in the Gulf War

Maria Rosario (Happy) G. Araneta, PhD
Assistant Professor, University of California at San Diego

Chairman Binns introduced the first presenter, Dr. Maria Rosario Araneta, to speak on her studies of birth defects and pregnancy outcomes following service in the Gulf War. (See Appendix – See Presentation 1.) Her presentation included the first release of the results from her study "Conception and Pregnancy During the Persian Gulf War: The Risk to Women Veterans" to be published in the November, 2003, issue of Annals of Epidemiology. A discussion took place following Dr. Areneta's presentation.

Dr. Golomb inquired about research showing problems that may not become apparent until children are older, including such concerns as behavioral problems. Dr. Araneta indicated that her studies had not been able to capture these problems given limitations associated with birth certificate data. She indicated that this type of problem had been recognized by CDC, which has considered monitoring possible birth-related problems though age six.

Dr. Haley complimented Dr. Araneta on the contributions of her studies. He asked if the study had compared birth defect rates in civilian versus military hospitals, since those who were ill might have left the service earlier. Dr. Araneta responded that the anonymous nature of birth defect registries prevented an ability to differentiate between births in military versus civilian hospitals.

Dr. Steele asked if rates of birth defects among female and male parents might be evaluated together rather than separately, as reported in Dr. Araneta's data. Dr Araneta replied that when rates in males and females were combined, three types of heart-related birth defects were significantly elevated.

Dr. Cherry noted that the rate of all birth defects combined was similar in the two groups. Dr. Araneta noted that overall birth defect rates in the U.S. had been fairly consistent over the last 20 years but that important discoveries about risk factors for birth defects requires that different types of birth defects be evaluated individually.

Dr. Golomb observed that separating the results for veterans who consider themselves ill would be useful to see if rates differed in ill vs. healthy veterans.

Mr. Graves suggested that future studies should consider differences in characteristics and locations of deployment.

Mr. Binns asked Dr. Araneta what future studies she would recommend. Dr. Araneta replied that she would recommend case control studies to evaluate these abnormalities and that future studies should also incorporate information related to exposures.

Mr. Binns asked what physicians should tell Gulf War veterans who may have concerns about having children. Dr. Araneta advised that veterans should be counseled to speak with their physicians and to take

folic acid three months prior to conception, as is recommended for any prospective parent with possible exposure risk.

Dr. Steele asked if Dr. Araneta had determined whether rates of birth defects had differed in different years following the war. Dr. Araneta replied that they had not looked at that.

Information From A Registry of Birth Defects in Children of Gulf War Veterans

Ms. Betty Mekdeci
Executive Director, Birth Defects Research for Children

Mr. Binns introduced the next speaker, Ms. Betty Mekdeci, Executive Director of Birth Defects Research for Children, a non-profit organization that maintains a registry of children of Gulf War veterans with birth defects. She presented data from the registry, as well as preliminary information from a cooperative study of Goldenhar Syndrome in children of Gulf War veterans. (See Appendix – Presentation 2.)

Following the presentation, Mr. Smithson asked how many of the veterans who are fathers of children within the birth defect registry are ill themselves. Ms. Mekdeci replied that she hasn't analyzed that yet, but the data were included in their questionnaire, and she will do it.

In response to a methodology suggestion, Ms. Mekdeci reiterated that the purpose of the registry is not the same as that of a research study.

Dr. Steele asked whether the questionnaire asked about exposures in theater. Ms. Mekdeci responded yes, but that many veterans don't know for certain what they were exposed to. Mr. Smithson wondered whether the questionnaire asked about veterans' locations in theater. Ms. Mekdeci said it did not, but that this information could be obtained in follow-up efforts.

Dr. Steele asked what denominators were used to estimate crude rates. Ms. Mekdeci replied that the information was obtained from Dr. Araneta's study.

Dr. Pellier asked if it is correct that Ms. Mekdeci had data on 40,000 families. Ms. Mekdeci clarified that information was available on 3,437 veterans' families. Dr. Pellier observed that, in the pharmaceutical industry when looking at the adverse effects of a drug, the comparison is done in relation to the overall population. He indicated that approach might be applied to the birth defect registry by comparing Gulf War veterans to the entire registry population, including Gulf War veterans. Ms. Mekdeci said that she would be interested to read references on this approach.

Dr. Cherry asked to what extent the cases in the registry included cases identified in Dr. Araneta's studies. Dr. Araneta replied that there were five in the Gulf War group and two in the nondeployed group.

Mr. Binns asked if Ms. Mekdeci planned to evaluate whether ill veterans are more likely to have children with birth defects than well veterans. Ms. Mekdeci said she could do that. Mr. Binns asked what research Ms. Mekdeci would recommend. Ms. Mekdeci emphasized the need to identify and assist families of female veterans who have children with birth defects.

The meeting adjourned for a brief break.

Findings on Birth Defects from the National Survey of Gulf War Veterans

Dr. Han Kang, MD, PhD
Director, VA Environmental Epidemiology Program/War-Related Injury and Illness Study Center
Washington, D.C.

Mr. Binns introduced Dr. Han Kang to present findings on birth defects from the National Survey of Gulf War Veterans that included recent results of medical record reviews done to determine the accuracy of veteran-reported birth defects in the study. (See Appendix – Presentation 3.)

After his presentation, Dr. Golomb observed that birth defect risks related to some exposures might increase over time, so it would be useful to do a similar data collection at a more recent point in time.

Dr. Haley complimented Dr. Kang for another great contribution to the literature. It was important to note that the veterans' self-reports appeared to be supported, and it would also be important to evaluate details related to the 17 that were not confirmed.

Mr. Robinson said he appreciated that self-reported surveys of veterans had been validated. He said he is receiving a large number of self-reports of veterans with multiple sclerosis. He also indicated that a recently released study implied that media perceptions affect self-reports.

Dr. Cherry noted that the only Achilles heel of the study would be if nondeployed veterans had higher rates of problems that had not been followed up. Were more self-reports not followed up in non-Gulf veterans? Dr. Kang replied that 33% of conditions were not followed up in non-Gulf and 40% of conditions were not followed-up in Gulf War veterans.

Dr. Araneta said that a military birth defects registry had been established in 1998 that was based on ICD-9 codes on birth certificates from military hospitals and births in civilian hospitals that had been paid for by the military. She indicated that this is a passive birth defect surveillance system, which typically underestimates birth defect rates by about 40%.

Dr. Kang said that the rate of birth defects in the nondeployed population in his study was similar to that found in the general population, suggesting that there had not been a problem of under-reporting in this group.

Ms. Mekdeci suggested asking parents for help in getting medical records.

Mr. Binns asked what future research Dr. Kang would recommend. Dr. Kang noted that the birth numbers were so small from Phase III of the National Gulf War Veterans Health Study that it was not possible to draw conclusions related to birth defect rates. To settle the issue, the study would have to have a considerably larger sample size, but that would be very expensive.

Mr. Binns asked if Dr. Kang has data to know whether the Gulf War veteran parents in his study were well or ill, and if it appeared that rates of birth defects had changed over time. Dr. Kang indicated that data collected for his study would allow them to look at both questions.

Dr. Haley suggested that selection bias might be reduced by looking at birth defects among all children in the family, not only the ones born first since the war. He also encouraged Dr. Kang to provide information on the total number of births in his cohort to other researchers who wish to study this problem. Dr. Kang thanked him for these suggestions.

Dr. Steele reviewed the recommendations regarding birth defects from the Draft Executive Summary of the Committee's upcoming report. Mr. Robinson suggested recommending active surveillance for birth defects to the military and noted that there are unspent funds available at DOD for future deployment health research. Dr. Araneta recommended that the State of California be allowed access to military hospital records. Dr. Steele asked about the nature of California's birth defect surveillance program. Dr. Araneta replied that it is a uniform system based on CDC codes.

Ms. Knox said that there should be a pamphlet to advise veterans who are considering having families about birth defects research.

Dr. Barlow asked if the Committee has authority to recommend better classification of birth defects.

Dr. Araneta said that there should be pregnancy-testing requirements prior to deployment. Ms. Knox indicated that those requirements currently are in place.

Dr. Steele noted that there is a very large study in Britain of birth outcomes among U.K. Gulf War veterans. Dr. Araneta said that the study results would be published in February 2004. Dr. Cherry said that the study includes all British deployed troops.

Mr. Smithson said that both ill and well veterans are concerned about whether veterans are at greater risk for having children with birth defects.

Dr. Araneta said that CDC is exploring the use of expanded ICD codes for birth defect surveillance.

Dr. Golomb observed that doctors often have so many requirements that they provide information on birth defects coding very quickly, resulting in high error rates for birth defects identified on birth certificates.

Ms. Mekdeci said it was important to follow through and look at defects that emerge later in a child's life.

Dr. Golomb cautioned that more research might change current impressions, just as findings from the research presented at this meeting differ from what was known two years ago.

Update on Published Research

Dr. Lea Steele, PhD
Scientific Director, RAC-GWVI

Mr. Binns welcomed Dr. Steele in her new dual capacity as scientific director of the Committee staff as well as Committee member. Dr. Steele presented an update on research published since the last Committee meeting. (See Appendix – Presentation 4.)

In the discussion that followed, Dr. Haley observed that there were two problems with the Hotopf study. First, it measured total serum paraoxonase levels, which are the wrong thing to measure. It should have measured the Q allozyme. Second, the case definition used in the study was far too broad and included people sick for any reason. This would result in the case group likely including people who are mildly symptomatic or ill for reasons unrelated to service in the Gulf War.

Regarding the Riddle article in Military Medicine, Mr. Robinson said that Dr. Mark Brown told him this information had been "state of the art" when this paper was put together several years ago. Dr. Golomb reviewed the premises cited in the article and showed they were no longer considered accurate. Mr.

Robinson said he had asked Dr. Brown if he planned to publish a retraction, and that he said he would if asked. Mr. Robinson suggested that the Committee should recommend a retraction. Mr. Graves agreed. Ms. Knox said that this publication is what military and VA physicians are reading.

Regarding the "Consensus Statement" paper, Dr. Meggs asked whether the authors mentioned that one of the common threads in many of the scenarios described was exposure to toxic elements. Mr. Robinson said that his veterans' organization had been aware of this effort to substantiate the stress theory. He expected that there would be objective evidence of illness in World Trade Center firefighters, too. Dr. Golomb agreed and pointed out that firefighting is also associated with toxic exposures.

The meeting adjourned for a lunch break

NTE and Identification of Possible Molecular Targets of Neurotoxic Exposures in Gulf War Veterans

Dr. Carrolee Barlow, MD, PhD
Director of Molecular Neurosciences, Merck Research Laboratory, San Diego, CA

Mr. Binns introduced the first speaker for the afternoon, Dr. Carrolee Barlow, who presented results of work conducted with colleagues at Salk Institute that demonstrated that neuropathic target esterase (NTE) is a target enzyme for organophosphates known to cause adverse neurological effects in humans. (See Appendix – Presentation 5.) This research may have implications for understanding the effects of these chemicals on humans and the potential role of genetic variability of this enzyme. Dr. Barlow also outlined the potential for genetic research to identify targets for developing treatments of potential benefit to both ill Gulf War veterans and others at risk of future terrorist or military chemical attack. Discussion followed.

Dr. Golomb asked if NTE is expressed in blood or saliva. Dr. Barlow said it is important to determine this in humans.

Dr. Soreq noted that AChE activity was also somewhat different in the NTE heterozygotes. Dr. Barlow thought this might be attributed to the small numbers in the study and thought it might not occur if a larger number were studied.

Dr. Pellier asked if Dr. Barlow had looked at NTE in the gut. Dr. Barlow said they had not, although they would be sending the mice to other researchers. Dr. Pellier asked if Dr. Barlow thinks that NTE is providing some type of maintenance of neurons and wondered if she had any related insights into other neurodegenerative diseases like Alzheimer's. Dr. Barlow said her sense is that Parkinson's may be linked to NTE.

Dr. Haley asked why the system doesn't recover when NTE levels are restored. Dr. Soreq stated NTE is a signaling enzyme.

Mr. Binns asked if Dr. Barlow could explain in layman's terms how the genetic research approach she described might lead to treatments. Dr. Barlow explained that once researchers find a gene and understand what its function is they can then screen pharmaceutical compounds to see what can affect the gene's product. She related that the gene for an orphan disease was identified by her group in 1998, and that they have now reached the point that they have identified a very promising drug compound. This was the timetable for an orphan disease affecting 1,000 children in the U.S., which is nowhere near the size of impact potentially associated with a better understanding of NTE.

Neurotoxins and Gulf War Illness: An Overview of VA's Research Enhancement Award Program (REAP)

Dr. Wilkie Wilson
VA Senior Research Career Scientist
Professor of Pharmacology, Duke University,

Mr. Binns introduced the next presentation by Dr. Wilkie Wilson providing an overview of VA's Research Enhancement Award Program (REAP) on neurotoxins and Gulf War illness. Dr. Wilson described the work of the VA-funded program, which will examine proteins expressed in patient and animal samples in relation to neuronal hyperexcitability and exposure to neurotoxins. This research has the potential to identify biomarkers that identify exposed individuals, as well as molecular targets for treatment interventions. (See Appendix – Presentation 6.)

Following he presentation, Dr. Golomb reported on a case of overexposure to organophosphates that was associated with seizures.

Dr. Barlow noted that she asked Dr. Steve Heineman at Salk Institute to look at NTE knockout mice to see if they were more susceptible to kindling. She also sent mice to Dr. Abou-Donia at Duke.

Mr. Robinson asked whether the PTSD difference mentioned by Dr. Wilson is caused by genetics or other protective mechanisms.

Dr. Golomb said that studies have shown that exposure to high levels of stress can affect the nervous system in a way that makes it hyperresponsive to later exposures.

Dr. Wilson observed that it might be beneficial to further study choline as a possible protective compound against the effects of exposure to acetycholinesterase inhibitors.

Dr. Golomb said it is important to determine if it might be used now to provide benefit to individuals who have already been injured.

Mr. Robinson commented that Special Forces troops are specially trained in measures to help them deal with extreme stress.

The meeting adjourned for a brief break.

Update on VA Gulf War Illness Research Programs

Dr. Nelda Wray, MD, MPH
Chief Research & Development Officer, U.S. Department of Veterans Affairs

Mr. Binns introduced the next speaker, Dr. Nelda Wray, VA's Chief Research and Development Officer (CRADO), and thanked her for her assistance in arranging for several of the speakers at the meeting.

Dr. Wray briefed the Committee on recently funded deployment health studies. She also presented information on plans for VA's Neuroimaging Resource Center and a Gulf War illness pilot project from the San Francisco VA. (See Appendix – Presentation 7.)

VA Study of AChE-R in Gulf War Veterans

Dr. Hermona Soreq, Hebrew University, Jerusalem, Israel
Dr. Steven Berkowitz, VA Cooperative Studies Program

Mr. Binns introduced Dr. Hermona Soreq who presented information on and preliminary results from the VA-sponsored study of acetylcholinesterase and other enzyme levels in Gulf War veterans. (See Appendix – Presentation 8.) Dr. Soreq's presentation was followed by a related presentation provided by Dr. Steven Berkowitz of VA's Office of Research and Development. The presentations were followed by discussion with Committee members concerning the study.

Mr. Robinson noted that there are blood samples for 900 veterans of Task Force Ripper, including both pre and post-Gulf War I samples. located at DOD. Dr. Craig Hyams would be familiar with the current disposition of these samples.

Dr. Cherry stated that the study design was not necessarily related to exposures in the Gulf War since someone with anxiety in the non-deployed group should be similar to someone with anxiety in the Gulf group.

Dr. Meggs asked whether the study was considering other symptoms of Gulf War illness besides anxiety such as cognitive dysfunction, memory loss, etc. Dr. Berkowitz replied that he was not sure of all the variables being studied and measures being used. They had measured anxiety with the Spielberger scale. Dr. Golomb stated that that scale is not useful for anxiety associated with physiological illness.

Mr. Binns asked if the group of Gulf War veterans whose samples were being studied include those with pain, cognitive difficulty, and other symptoms other than anxiety. Dr. Berkowitz said yes. All of those data were collected, including all symptoms endorsed by the veterans.

Mr. Graves commented to Dr. Soreq that when she had last presented information on AChE-R to the Committee, he believed that her work was on the verge of leading to treatment options for those with excess levels of AChE-R. He asked about the current status of those efforts. Dr. Soreq responded that treatments tested for a particular condition must be shown to be relevant to that condition. Dr. Berkowitz stated that by the end of the study, we will know if AChE and AChE-R levels are related to Gulf War illness.

Mr. Binns asked if they would have data in February on just anxiety or on the full range of symptoms. Dr. Berkowitz replied that he would expect to have the full range.

Mr. Graves asked why VA had focused this study on anxiety in the first place. Dr. Berkowitz replied that Dr. Soreq had previously done work in a U.S. population that showed an association of anxiety with AChE-R.

Dr. Cherry then asked why the study was not addressing the central hypothesis put forward by Dr. Soreq and the Committee when the study was recommended. Dr. Berkowitz replied that the hypothesis of the study was that anxiety may have produced veterans' symptoms. Dr. Cherry reiterated that that had not been the hypothesis put forward by the Committee and recommended for study.

Dr. Golomb stated that studies have clearly shown that a relatively small number of ill veterans have anxiety.

Dr. Haley observed that the Iowa study, from which this group of veterans was drawn, was conducted by piecing together questions from various studies. As a result, they have reported findings that are very different from other studies, including a higher estimate of problems with anxiety than has been found in other studies. The interest of the Committee was that enzyme levels be assessed in the larger group of veterans who have Gulf War illnesses, but do not have anxiety. Dr. Berkowitz said that these individuals should be factored out.

Dr. Golomb said that many Committee members were uncomfortable with what Dr. Berkowitz was saying. In the past, when researchers have found symptoms of psychological difficulties in ill veterans, the findings were used to say that Gulf War illnesses are the result of stress. The Committee had been interested in evaluating physiological parameters of Gulf War illness. Dr. Berkowitz said that it is important to isolate the differences associated with each factor. Dr. Golomb replied that the approach described by Dr. Berkowitz would not be capable of doing that, since it relies on the assumption that anxiety caused the physiological symptoms when the physical symptoms could have, in fact, caused anxiety symptoms experienced by ill veterans. Dr. Steele agreed, indicating that the study design was the tail wagging the dog and that there was no evidence from previous research indicating that anxiety had caused all the other symptoms experienced by veterans.

Dr. Barlow said that although she is an outsider, she understands where the Committee's concern is coming from. It was important that the populations to be studied be properly defined, and then that the data be allowed to speak for itself. Dr. Berkowitz replied that even if the premise of the study was erroneous, the study findings might still provide the justification for a clinical trial.

Dr. Golomb asked Dr. Soreq if she thought that the primary issue of interest for Gulf War illnesses related to anxiety. Dr. Soreq replied that she thinks that the most prominent link with AChE-R is with neuromuscular disease.

Dr. Cherry said she thought we were looking at a marker for exposure but that the purpose of the study had somehow been twisted, changed to a test of anxiety. Dr. Barlow commented that "healthy individuals with anxiety" was not a tight definition for a population to be studied. Dr. Steele said the Committee had expected the purpose of this work was to measure whether veterans with Gulf War illness had elevated AChE-R levels. Dr. Golomb reiterated that anxiety, as a symptom, is present in a very low number of ill veterans. Dr. Barlow said that because ill Gulf War veterans do not look anything like a group of people with anxiety disorders, she thought the anxiety aspect of the study should be scrapped.

Dr. Berkowitz replied that as far as he knew, all of the data would be looked at.

Dr. Haley said there needed to be a protocol people agree on.

Dr. Pellier asked if VA and the study leaders would submit an analysis plan to the Committee. Dr. Berkowitz replied that he would have to discuss that with the research leadership and the principal investigators. Dr. Cherry asked if the committee could see the current analysis plan tomorrow. Dr. Berkowitz said he did not have a copy of the analysis plan.

Public Comment – Day 1

Mr. Binns stated that the next agenda item was the public comment period and called on the individuals who had signed up to provide comments.

Alison Johnson said that in a study of multiple chemical sensitivity (MCS) in Atlanta, 1.8% of those with MCS reported having psychiatric symptoms before they developed MCS and 38% reported having psychiatric symptoms after they developed MCS. She also reported that results of using neurotin for MCS have been terrible. She indicated that some individuals with MCS had reported good results with its use early on but had later crashed, and that the drug had been difficult to withdraw from.

Denise Nichols said that, if you talk to the vets, they are still generally being treated as psychiatric patients in the VA system. It also concerned her that the death rate was still going up. She wondered how many who died were given psychiatric treatments when they should have been given medications for their medical problems. She knew, for example, of individuals put on heavy psychiatric medication when they had chest pains. An ill friend who went with her to a conference and forgot his medications was much better when he did not take the drugs. She asked to know what doctors are seeing at the specialty clinics where Gulf veterans are sent. She said she was not asking for a study, just information and communication.

Mr. Binns thanked the members of the public for their comments.

The meeting adjourned for the day at approximately 5:15 p.m.

The meeting reconvened the following day, October 28, 2003, at 8:30 a.m.

Department of Defense (DOD) Research on Gulf War Veterans' Illnesses and Chemical Defense

Dr. Michael Kilpatrick, Deputy Director, DOD Deployment Health Support Directorate
Dr. Robert E. Sheridan, U.S. Army Chemical Defense Institute
LTC (Dr.) Brian Lukey, Director, U.S. Army Military Operational Medicine Research Program

Mr. Binns introduced Dr. Michael Kilpatrick. Dr. Kilpatrick presented a briefing on DOD's medical research program, including research on Gulf War illnesses and deployment health, and an overview of DOD research relating to chemical defense. (See Appendix – Presentation 9.) This was followed by a presentation by Dr. Robert E. Sheridan of the Army Chemical Defense Institute (See Appendix – Presentation 10.) A discussion followed during which LTC Brian Lukey joined Drs. Kilpatrick and Sheridan in responding to questions about the DOD programs presented.

Mr. Binns asked LTC Lukey and Dr. Sheridan about funding levels for their programs. He noted that one of the researchers who presented to the committee the previous day, whose research has been funded by the Chemical Defense Institute for many years and is highly regarded, had been advised that no funds were available to continue the research. This situation appeared to make no sense at a time when the country is more concerned about chemical defense than at any previous time in its history.

Dr. Sheridan replied that funding for medical chemical defense research was down this year compared to last year and that the overall trend over several years had been flat. In FY2003, the program funded only intramural projects, and was not able to fund all intramural studies planned. In the current year intramural projects are competing with extramural, but funds are still very tight because many of last year's studies are committed over two years.

LTC Lukey noted that the scientific panels that advise on his programs' research have all expressed the judgment that their various areas of research are inadequately funded.

Dr. Golomb commented on the importance of drawing and maintaining whole blood samples before and after the current deployment in Iraq and future deployments.

Mr. Robinson asked LTC Lukey if the pre- and post-Gulf War I blood samples from Task Force Riper could be used for testing. LTC Lukey replied that he would be interested to see what tests are available and that it is important that the best tests were identified before using scarce stored blood.

Dr. Steele asked why the Department of Defense was no longer funding research on Gulf War Illnesses at the very time when the research is beginning to provide important insights. It would also seem that Gulf War veterans are a large group that can be studied to provide important insights in relation to future deployment and domestic concerns. Dr. Kilpatrick replied that there is some continuation of Gulf War-related research.

Additional Findings from the VA ALS Study and Update on the ALS Registry

Dr. Eugene Oddone, MD, MHSc
Director, Health Services Research Center, Duke University

Mr. Binns introduced Dr. Eugene Oddone to present additional findings from VA's ALS Study and to update the committee on VA's ALS registry. (See Appendix – Presentation 11.) A discussion followed.

Mr. Binns asked if results of the interviews regarding exposures showed any relationship between exposures and ALS, noting that there have been at least two anecdotal reports of ill Gulf War veterans developing ALS after secondary exposures to pesticides. Dr. Oddone replied that Dr. Peter Spencer had not found any associations of ALS with deployment-related exposures. His analyses did not address exposures after deployment.

Ms. Knox asked if Dr. Oddone's team still had the blood samples from the study. Dr. Oddone replied yes.

Mr. Robinson said that veterans calling in to the National Gulf War Resource Center are reporting multiple cases of multiple sclerosis (MS). Might the ALS Registry also look at MS in the future? Dr. Oddone reported that his group had also received calls on MS but that there was no one to hand them off to in the VA system. Mr. Smithson asked if they are maintaining a list of MS patients. Dr. Oddone stated that they were not documenting MS cases at this time.

Dr. Golomb added that she had also heard of cases of MS among Gulf War veterans. Dr. Steele stated that there is an online group of Gulf War and other veterans who have MS, but that there were currently no research efforts focused on the question of MS rates in Gulf War veterans.

Dr. Pellier commented that the ALS study is very important. It provided the first tangible evidence of neurodegenerative disease in Gulf War veterans. He thinks it would be useful to look at all neurodegenerative diseases including ALS, MS, and Parkinsons Disease. Dr. Oddone said they could widen the scope of the effort to include MS and Parkinsons and that such an effort should not triple the total cost.

Mr. Graves asked if anyone has contacted the Kuwaitis to see if they had been affected by excess rates of neurodegenerative diseases. Dr. Oddone said they hadn't, but that it was a good idea. Mr. Graves said that Kuwait might also be a source of funding for that type of research. Mr. Robinson said that the Kuwait government had put out a call for researchers to do health studies on Kuwaitis.

Dr. Steele asked if they were also including veterans with ALS who had died in order to construct an epidemiologic curve. Dr. Oddone said that initial calculations suggested that the epidemiologic curve had already peaked.

Dr. Steele asked about cases of neurodegenerative diseases referred to the registry that had ultimately not been verified as ALS cases, and what had been the types of conditions in this group. Dr. Oddone said that he could get that information.

Dr. Cherry asked about DNA findings evaluated for the study. Dr. Oddone said he did not have that information, but it would be included in a future manuscript.

Dr. Haley asked if there has been discussion of a brain bank to archive tissues of patients who had died. Dr. Oddone said yes, that they had obtained cost estimates on rapid autopsies that had been about $5,000 per patient. He said they would be working with patient groups.

Monitoring the Health of Gulf War Veterans Using Existing VBA Data Systems

Ms. Susan Perez
Asst. Director, Data & Information Services, Office of Performance Analysis & Integrity
U.S. Department of Veterans Affairs

Mr. Binns introduced Ms. Susan Perez. She presented information on benefits claims data resources at the Veterans Benefits Administration (VBA). (See Appendix – Presentation 12.) In particular, she presented data that had been requested by the Committee concerning: (1) the number of veterans who had submitted disability claims and had served in the Gulf War, and the number of veterans who had submitted disability claims who had been in the military during the Gulf War but had not deployed to the Persian Gulf theater; (2) the demographic and military profiles of the two groups; and (3) the number and proportion of individuals from the two groups who had submitted claims for three conditions: ALS, multiple sclerosis, and tinnitus.

Figures reported in response to these data requests were shown in the presentation slides. Although no statistical analyses were provided, the figures did not indicate that a larger proportion of Gulf War veterans had submitted disability claims for MS than veterans who had not served in the Gulf War. Ms. Perez cautioned that this information was not a complete count of MS cases in either group and should not be over interpreted due to limitations inherent in data relating to disability claims.

A discussion followed. Dr. Steele commended Ms. Perez for her teams' efforts in preparing the GWVIS reports and their demonstration of the different types of data available at VBA that might be helpful in monitoring the health of Gulf War veterans.

Monitoring the Health of Gulf War Veterans Using VHA Data and Information Resources

Dr. Denise Hynes
Director, Information Resource Center, U.S. Department of Veterans Affairs

Mr. Binns introduced Dr. Denise Hynes, who joined the meeting by telephone from Illinois. Dr. Hynes presented information on the databases and resources available at VA's Veterans Health Administration (VHA). (See Appendix – Presentation 13.) Due to technical problems with the teleconference equipment, Dr. Hynes was unable to hear questions from Committee members, so minimal discussion occurred following her presentation. Mr. Binns thanked Dr. Hynes for her presentation, and the meeting adjourned for lunch.

Anthrax Vaccinations and Health Outcomes in the National Survey of Gulf War Veterans

Dr. Claire Mahan
Environmental Epidemiology Service, U.S. Department of Veterans Affairs

Mr. Binns introduced Dr. Claire Mahan, who presented results from VA's National Survey of Gulf War veterans including a subgroup of veterans known to have received the anthrax vaccine in association with Gulf War deployment. (See Appendix – Presentation 14.) A discussion followed.

Dr. Golomb observed that the apparent findings related to self-reported receipt of the anthrax vaccine may reflect instead those who received multiple vaccinations.

Dr. Cherry asked if they had controlled for confounding factors related to deployment. Dr. Mahan said they had controlled for a number of confounding factors, and that one important factor was that more than 70% of the subset of veterans with DOD shot records had been in the National Guard.

Dr. Haley noted that the study findings indicated a recall bias and asked if there might be a way to assess the degree of bias and adjust for it. Dr. Golomb stated that that probably couldn't be done without having more information than was available.

Dr. Steele asked for information about who was in the subset of veterans with shot records, and where those records had come from, since it had generally been assumed that there were no records of who had received the anthrax vaccine. Dr. Mahan and an audience member from DOD indicated that there were records available for a few units.

Mr. Robinson noted that this data limitation illustrated the importance of careful monitoring of the health of current troops after they received vaccines.

Dr. Cherry said she had found similar results in her study of UK veterans. When analyses took into account other experiences in theater, preliminary associations of symptoms with the anthrax vaccine disappeared. .

Federal Trials of the Anthrax Vaccine

Dr. Jack Melling
Director, Karl Landsteiner Institute, Vienna

Mr. Binns introduced Dr. Jack Melling, consultant to the committee, to present an update on federal trials of the anthrax vaccine. (See Appendix – Presentation 15.) A discussion followed.

Dr. Melling noted that studies of newer types of anthrax vaccines being studied often include a comparison group that receives anthrax vaccine adsorbed (AVA), the type of vaccine currently used by the military. Long-term evaluation of symptoms reported by participants in this arm of vaccine trials could provide the type of information the Committee thinks should be collected with respect to whether AVA is associated with long-term adverse effects.

In the discussion that followed Dr. Melling's presentation, Mr. Robinson said that the U.S. Senate has passed a Sense of Senate resolution to stop the current vaccination program. Lawsuits are pending.

Dr. Steele asked Dr. Melling to explain the difference between AVA and the newer recombinant protective antigen (rPA) vaccines being developed. Dr. Melling replied that AVA is a 1950's vaccine.

The organism is grown and filtered, and the protective antigen (PA) is isolated for use in the vaccine. The process results in a lower purity of PA, with the specific amount varying from batch to batch. The newer rPA vaccines use the gene that codes for the anthrax antigen and puts it into another organism. This process provides a higher purity and better control of antigen levels.

Mr. Robinson said that his understanding for the current deployment was that some blood samples were taken prior to the shots being given and that samples will be collected again at a later time. He believed that the Army was doing a limited surveillance for the vaccine's effects and he understood this was being done at Walter Reed.

Dr. Melling said that the relevant parts of the new vaccine studies being planned had not been designed yet, and it might be possible for the Committee to find out more about the details and to make specific suggestions with respect to follow-up.

Mr. Robinson observed that the current vaccine is a different vaccine from the one used in Gulf War I. Dr. Golomb agreed, but said that if studies of the newer vaccine showed a problem, it had some relevance.

Committee Business

Mr. Binns stated that the next topic for consideration was committee business. Dr. Steele presented a proposed plan of work for the committee and staff over the coming year. (See Appendix – Presentation 16.) Committee members expressed approval of the plan and provided comments on various aspects of committee activities.

Dr. Golomb said that the topics chosen for meetings and speakers should include areas related to our hypotheses relating to the causes and pathophysiology of Gulf War illnesses.

Mr. Robinson emphasized that treatments were an important area to consider on an ongoing basis.

Mr. Graves asked what funding the committee had. Mr. Binns replied that the committee's own budget remained at $400,000.

Dr. Melling suggested that speakers could be invited to make written submissions in advance of the meeting which could be posted to the website.

Dr. Steele suggested that the agenda might include public comments on only one day of each meeting, and invite members of the public who provide comments to submit them in writing for the permanent record.

Mr. Smithson asked about the visibility of the website and whether we could keep track of visits? Dr. Steele replied that she had asked VA to do this, and they were working on it.

Dr. Steele raised the subject of the degree to which the committee should consider issues arising out of the current Iraq deployment. Dr. Golomb said that the committee should stay focused on Gulf War I and that evaluating issues related to the current deployment could dilute the Committee's efforts. The purpose for which the Committee had been established was the illnesses affecting Gulf War I veterans. Dr. Haley said Gulf War I has never ended for those ill veterans and that there may not be much we can do for Gulf

War II veterans at this point in time. Dr. Cherry said that we can keep informed of issues relating to the current war, but may not feel qualified to make recommendations.

Mr. Robinson noted that there are 600 soldiers currently at Fort Stewart with health problems from Afghanistan and Iraq and that the Committee could make recommendations based on lessons learned. Dr. Golomb agreed. Mr. Robinson said the U.S. Senate would be holding hearings on this issue and that others would be working on it as well. Given the considerable experience of some of the Committee members, it might be possible to make some simple recommendations related to things that should be done in relation to the current deployments. Veterans expect the Committee to provide information that helps 1991 Gulf War veterans and also helps make sure that the types of problems they have experienced do not happen again.

The consensus of the discussion was that the Committee would write a letter to Secretary Principi updating an earlier letter regarding lessons learned. Mr. Robinson indicated he would provide the first draft for Committee consideration.

Ms. Knox asked if there are samples of the anthrax vaccine used during the first Gulf War. Mr. Robinson's understanding was that no samples had been saved.

Mr. Robinson said he is interested in choline as a prospective treatment. Dr. Golomb agreed.

Dr. Melling saw a need to provide current information to VA clinicians that might serve to "reprogram" them away from focusing so much on psychiatric explanations and treatments for Gulf War illnesses. Dr. Steele said this could be a topic for a future meeting.

Mr. Graves said information relating to oil well fires should be considered. For Gulf War veterans located in the middle of the oil well fires, it was like living in a fishbowl of oil rain.

Mr. Robinson said that sand also may have been a factor, and that it could have acted as a carrier for some of the other exposures of concern such as pesticides, infections, and depleted uranium.

There was applause following the discussion of the proposed topics to be addressed at 2004 meetings. The discussion then turned to communications maintained by the Committee. Dr. Steele described summaries of recently-published research and other matters of interest relating to Gulf War illnesses that would be provided to Committee members on a regular basis. Dr. Meggs said that members should continue to chat back and forth by email about emerging research information. Dr. Steele agreed that organized reports should not block the free flow of information. Ms. Knox asked if this information might also be provided to veterans. Dr. Steele indicated it could be put on the Committee's website.

Dr. Cherry said that the upcoming report to the Secretary should include a focus on treatments. It also should reinforce the need to use and merge existing databases. Ms. Knox asked about the types of links needed between different data sources. Dr. Steele noted that to the best of her knowledge, the presentations made earlier in the day were the first opportunity for VBA to learn about databases available at VHA.

Mr. Robinson said that the Senate and House Armed Services and Veterans Committees should receive testimony on the Committee's report. That may be the best way to launch it. The Secretary could request a hearing with those committees.

Dr. Golomb asked about the possibility of publishing a position paper in a medical journal. Dr. Steele noted that the PAC and NIH committees had published articles relevant to their major findings.

Mr. Robinson suggested seeking a Sense of Congress resolution.

Dr. Cherry said that an article in Military Medicine might be a good idea. A short piece would do, or a letter to the editor. Dr. Golomb said that one of the major journals is another option.

Public Comment – Day 2

Venus-val Hammack said that the publication U.S. Medicine is also commonly read by VA doctors. Regarding treatments and education through VA, Mark Brown had produced a guide for physicians on Gulf War illnesses, but half of the Persian Gulf coordinators at VA facilities do not have copies. She suggested that the Committee look at this guide, which is at least three years old.

Alison Johnson said a recent article in Sociology had some chilling information. Soldiers who applied to sick call were assigned to unpleasant duty. She offered her video and book for VA training and indicated they had been well received. She offered to make a master copy available for anyone to copy for free or to sell copies for $3.00. She is trying to raise $2,500 for insurance so PBS local stations can show the video.

Denise Nichols commented that the Committee had done some great work. However, the holiday season was coming up and the journals have had some discouraging reports. She wondered if the Committee could do an update, even on a website, of encouraging news such as the partial results from Israel? Suicides increase at the holiday season. Dr. Golomb asked if veterans put the word out to other veterans. Ms. Nichols said that there is a need to get the word out to VA clinicians, perhaps through teleconferencing. She said that VA should start turning things around for the veterans and that although the Committee had done good work with hard research and she was thrilled that treatments would be addressed, it was important to find a way to make a difference a little quicker for sick veterans. Ms. Nichols said that "where the pedal hits the metal" out there at VA hospitals, they still don't get it. They think Gulf War illness is psychological and refer ill veterans to psychiatrists. Ms. Knox observed that she had a good point.

Mr. Robinson noted that the Committee has no presence in any VA publication. Dr. Steele said that information on the Committee had been published in VA's Persian Gulf Review.

Dr. Cherry said that inviting written public comments was a good idea.

Mr. Robinson advised the Committee that the annual National Gulf War Resource Center conference would be held April 30, May 1, and 2, 2004 in Washington, DC. The conference would include a tour of the WRIISC Center and the clinical center at Walter Reed.

The meeting adjourned at approximately 4:00 p.m.

Appendix

Presentation 1- Maria Araneta

Birth Defects and Pregnancy Outcomes Following Service in the Gulf War

Maria Rosario (Happy) G. Araneta, Ph.D.

October 27, 2003

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

Prevalence of Birth Defects Among Infants of Gulf War Veterans in Arkansas, Arizona, California, Georgia, Hawaii, and Iowa, 1989-1993

Birth Defects Research (Part A): Clinical and Molecular Teratology 2003: 67;246-260

Authors:

Maria Rosario G. Araneta	NHRC
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Charlotte A. Hobbs	Arkansas
Timothy J. Flood	Arizona
John A. Harris	California
Diane Krishnamurti	Iowa
Gregory C. Gray	NHRC

Background

- U.S. General Accounting Office: 21 teratogens and reproductive toxicants present in the GW environment
- *Oil fires and soil:*

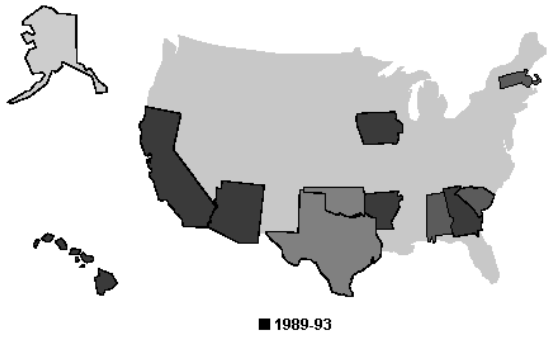
  arsenic benzene benzopyrene
  cadmium lead mercury
  nickel toluene xylene
  di-n-butyl phthalate hexachlorobenzene
  hexachloroethane pentachlorophenol
  hexachlorocyclopentadiene
- *Pesticides:*

  carbaryl diazinon dichlorvos
  ethanol lindane warfarin
- *Decontaminating agents:*
  ethylene glycol monomethyl ether

Previous studies

- *Penman, 1996: 2 National Guard units, 5 case infants*
- *Cowan, 1997: military hospitals, newborn diagnoses only, ICD-9 codes*
- *Araneta, 1997: Goldenhar syndrome, military hospitals, rare condition*
- *Goss Gilroy, Inc. 1998: Canada, self-reported, ↑ birth defects among GWV infants*
- *Kang, 2001: self-reported, not validated against medical records, ↑ birth defects among GWV infants*

States with Active Surveillance for Birth Defects



Active Case Ascertainment for Birth Defects

1. Population-based
   - includes military and non-military hospitals
   - births to Reservists and National Guard members
   - births to former military personnel
2. Surveillance through infant's 1st birthday
   - Captures 95%-99% of birth defects

Active surveillance of Birth Defects

3. Data abstracted from multiple sources:
   outpatient clinics *hospitals*
   cytogenetic laboratories *genetic clinics*
   cardiac catheterization logs *surgical logs*
   molecular biology laboratories
4. Birth defects recorded by CDC's 6-digit code for Reportable Congenital Anomalies
5. Provides more complete case ascertainment and morphologic classification of birth defects

Objectives

- Identify infants born to military personnel between 1989-93 in states with active surveillance of birth defects

- Measure the prevalence of selected birth defects

a) GWV and NDV infants
   - prewar conceptions
   - postwar conceptions

b) GWV infants
   - prewar vs. postwar conceptions

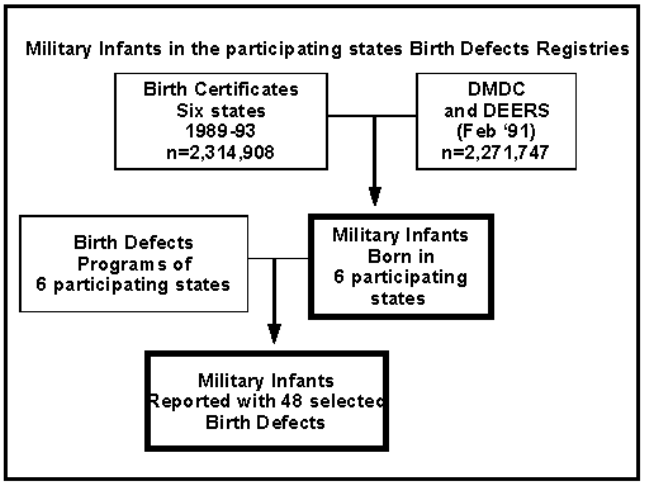
Methods - Data Sources

Military:

- Defense Manpower Data Center (DMDC) - *military sponsor data*
- Defense Eligibility Enrollment Reporting System (DEERS) – *spouse, children*

Arkansas, Arizona, California, Georgia, Hawaii, Iowa:

- Vital records - *birth certificates*
- Birth Defects Programs - *birth defects data*



48 Selected Birth Defects

Anencephalus	Spina Bifida
Hydrocephalus	Encephalocele
Microcephalus	
Aniridia	Congenital cataract
Anophthalmia/microphthalmia	
Anotia/microtia	
Cleft palate	Cleft lip

48 Selected Birth Defects (continued)

Common truncus
Ventricular septal defect
Aortic valve stenosis
Pulmonary valve atresia/stenosis
Pulmonary valve insufficiency
Endocardial cushion defect
Pulmonary artery anomalies
Transposition of great arteries
Tricuspid atresia/stenosis
Tricuspid valve insufficiency
Hypoplastic left heart syndrome
Tetralogy of Fallot
Ebstein's anomaly
Coarctation of aorta

48 Selected Birth Defects (continued)

Lung agenesis/hypoplasia
Choanal atresia

Pyloric stenosis
Biliary atresia
Diaphragmatic hernia
Hypospadias/epispadias
Renal agenesis/hypoplasia
Obstructive genitourinary defect
Esophageal atresia/tracheoesophageal fistula
Rectal/large intestinal atresia/stenosis
Hirschsprung disease
Gastroschisis
Omphalocele
Bladder exstrophy

48 Selected Birth Defects (continued)

Reduction deformity - upper limbs, lower limbs
Trisomy 13 (Patau syndrome)
Trisomy 18 (Edward syndrome)
Trisomy 21 (Down syndrome)

Fetal alcohol syndrome
Amniotic bands

Dextrocardia
Chromosomal anomalies
Goldenhar syndrome (oculoauriculovertebral complex)

Estimates of Prewar and Postwar Conceptions

Prewar conceptions:
GW: Infant's DOB ≤ Mother's deployment date
Infant's DOB - gest. age ≤ Father's deploy date
NDV: Conceived ≤ December 31, 1990

Postwar conceptions:
GW: Infant's DOB > Mother's deployment date
Infant's DOB - gest. age ≥ Father's return date
NDV: Conceived ≥ January 1, 1991

Table 1. Demographic Characteristics of Infants Born to Women Military Personnel, 1989-93

	GWV (n=450)	NDV (n=3,966)
Male	48%	50%
Birthweight (gms)	3,351	3,341
Preterm birth (<37 wks)	9%	9%
Maternal age (yrs)	25.3	25.9*
Paternal age (yrs)	27.2	27.5
White	51%	60%*
≤ High school	55%	53%
Unmarried	28%	23%*

*p-value<0.05 (statistically significant)

Demographic Characteristics of Infants Born to Women Military Personnel, 1989-93

	GWV (n=450)	NDV (n=3,966)
Smoking	7%	9%
Alcohol	1%	1%
Prenatal visits	11.2	11.7*
Army	64%	35%*
Marine Corps	11%	5%*
Reservist/Natl Guard	24%	12%*
Military Officers	8%	11%*

*p-value<0.05

Table 2. Demographic Characteristics of Infants Born to Male Military Personnel, 1989-93

	GWV (n=11,511)	NDV (n=29,086)
Birthweight (gms)	3,367	3,389*
Maternal age (yrs)	25.3	26.0*
Paternal age (yrs)	26.6	27.5*
White (mother)	59%	63%*
≤ High school (mother)	56%	51%*
Unmarried	10%	7%*
Prior live births	0.8	0.9*
Multiple births	1.8	2.4*

*p-value<0.05

Demographic Characteristics of Infants Born to Male Military Personnel, 1989-93

	GWV (n=450)	NDV (n=3,966)
Marine Corps	28%	11%*
Enlisted personnel	83%	78%*

*p-value<0.05

Table 3. Selected Birth Defects Prevalence* among Prewar conceptions to Women GWVs and NDVs,1989-91

	GWV (n=142)	NDV (n=2,007)	RR (95%CI)
Hydrocephalus	1 (70)	2 (10)	7.1 (0.6-79)
VSD	0	11 (55)	
Obstructive genitourinary defect	0	6 (30)	
Pyloric stenosis	0	5 (30)	
Hypospadias	0	5 (30)	
Tetralogy of Fallot	0	4 (20)	
Cleft lip w/o c.palate	0	3 (15)	

per 10,000 live births

Table 4. Selected Birth Defects Prevalence* among Prewar conceptions to Male GWVs and NDVs,1989-91

	GWV (n=6,863)	NDV (n=17,922)	RR (95%CI)
Hypospadias	22 (32)	51 (29)	1.1 (0.7 - 1.9)
Pyloric stenosis	14 (20)	25 (14)	1.5 (0.8 - 2.8)
VSD	13 (19)	45 (25)	0.8 (0.4 - 1.4)
Obstructive genitourinary defects	9 (13)	29 (16)	0.8 (0.4 - 1.7)
Down syndrome	9 (13)	21 (12)	1.1 (0.5 - 2.5)
Tricuspid valve insufficiency	8 (18)	24 (20)	0.9 (0.4 - 2.0)
Aortic valve stenosis	0	4 (2)	

per 10,000 live births

Table 5. Selected Birth Defects Prevalence* Among Postwar Conceptions to Women GWVs and NDVs,1991-93

	GWV (n=308)	NDV (n=1,959)	RR (95%CI)
Hydrocephalus	1 (32)	1 (5)	6.4 (0.2 - 189)
VSD	1 (32)	7 (36)	0.9 (0.05 - 5.5)
Pulm valve atresia	1 (32)	1 (5)	6.4 (0.2 -189)
Cleft lip	1 (32)	1 (5)	6.4 (0.2 -189)
Hypospadias	4 (130)	4 (20)	6.4 (1.5 - 27)†
Renal agenesis	1 (32)	3 (15)	2.1 (0.1 - 18)
Obst genitourinary	1 (32)	8 (41)	0.8 (0.04 - 4.7)
Down syndrome	1 (32)	0	

per 10,000 live births; †p= 0.015

Table 6. Selected Birth Defects Prevalence* Among Postwar Conceptions to Male GWVs and NDVs,1991-93

	GWV (n=4,648)	NDV (n=11,164)	RR (95%CI)
Hypospadias	15 (32)	35 (31)	1.0 (0.6 - 2)
VSD	10 (21)	36 (32)	0.7 (0.3 - 1)
Tricuspid valve insufficiency**	10 (29)	9 (11)	2.7 (1.1 - 7)†
Obst genitourinary	9 (19)	21 (19)	1.0 (0.5 - 2)
Pyloric stenosis	7 (15)	18 (16)	0.9 (0.4 - 2)
Aortic valve stenosis	5 (11)	2 (2)	6.0 (1.2 - 31)‡
Coarctation of aorta	5 (11)	3 (3)	4.0 (0.96-17)
Renal agenesis	5 (11)	5 (4)	2.4 (0.7 - 8)

*per 10,000 live births, ** California births excluded,*
†p=0.039, ‡p=0.026

Table 7. Selected Birth Defects Prevalence* Among Prewar vs. Postwar conceptions to Women GWVs,1989-93

	Postwar (n=308)	Prewar (n=142)	RR (95%CI)
Hydrocephalus	1 (32)	1 (70)	0.5 (0.03 - 7)
VSD	1 (32)	0	
Pulm valve atresia	1 (32)	0	
Cleft lip	1 (32)	0	
Hypospadias	4 (130)	0	
Renal agenesis	1 (32)	0	
Obst genitourinary	1 (32)	0	
Down syndrome	1 (32)	0	

**per 10,000 live births*

Table 8. Selected Birth Defects Prevalence* Among Prewar vs. Postwar conceptions to Male GWVs,1989-93

	Postwar (n=4,648)	Prewar (n=6,863)	RR (95%CI)
Hypospadias	15 (32)	22 (32)	1.0 (0.5 - 2)
VSD	10 (21)	13 (19)	1.1 (0.5 - 3)
Tricuspid valve insufficiency**	10 (29)	8 (18)	1.6 (0.6 - 4)
Obst genitourinary	9 (19)	9 (13)	1.5 (0.6 - 4)
Pyloric stenosis	7 (15)	14 (20)	0.7 (0.2 - 2)
Aortic valve stenosis	5 (11)	0	16 (0.9 - 294)†
Coarctation of aorta	5 (11)	1 (2)	7.4 (0.9 -63)
Renal agenesis	5 (11)	0	16 (0.9 - 294)†

** per 10,000 live births; † p<0.011 logit estimator*

Adjusted Prevalence – cardiovascular defects

↑ tricuspid valve insufficiency and aortic valve stenosis did not differ when adjusted by:

- State
- Maternal and paternal age
- Ethnicity
- Marital Status
- Education
- Parity, multiple births
- Prenatal visits
- Military branch, rank

Adjusted Prevalence – hypospadias

↑ Prevalence of hypospadias persisted after adjustment for:

- Paternal age
- Small for gestational age
- Low birth weight
- Preeclampsia
- Low parity

Adjusted Prevalence – renal agenesis or hypoplasia

↑ Prevalence of renal agenesis/hypoplasia persisted after adjustment for:

- Prenatal alcohol
- Intrauterine growth retardation

Conclusions

- Linkage of military and state health department records enables measurement of the prevalence of birth defects among infants:
  - Through infant's 1st year of life
  - in military and civilian hospitals
  - Reservists and National Guard members
  - former and current military personnel
- Higher prevalence of tricuspid valve insufficiency, aortic valve stenosis, and renal agenesis/hypoplasia in postwar infants of GWV men.

Conclusions

- Higher prevalence of hypospadias among postwar infants of GWV women.
- The etiology of birth defects is unknown for 70% of all birth defects
- We did not have the ability to determine if the excess risk of birth defects was cased by inherited, environmental, or synergistic factors, or was due to chance.

Limitations

- California: no access to military hospitals
- Limited to live births
- Birth defects diagnosed after first birthday not included (1% - 5%)
- Statistical power
- Multiple comparisons

Statistical Power

Condition	Optimum sample size	Available
Hypospadias	257	154
Statistical power	80%	67%
Tricuspid valve insuff.	6373	4648

Multiple Comparisons

Comparisons	Expected	Observed
Postwar GWV vs NDV women		
7 birth defects	0.35	1
Postwar GWV vs NDV men		
26 birth defects	1.3	2
Postwar GWV vs prewar GWV men		
24 birth defects	1.2	2

Conception and Pregnancy during the Persian Gulf War: The Risk to Women Veterans

Annals of Epidemiology, November 2003

Araneta MRG, Kamens DR, Zau AC, Gastanaga VM, Schlangen KM, Hiliopoulos KM, Gray GC.

Purpose

To characterize reproductive outcomes:

- Live births
- Stillbirths
- Spontaneous abortions
- Ectopic pregnancies
- Induced abortions

among women who were pregnant while deployed to the Gulf War

Methods

- Deployment data + inpatient records (153 military hospitals) were used to identify servicewomen who were:
  - pregnant between August 1990 and May 1992
  - belonged to UIC deployed to the Gulf War
- Postal surveys in 1997-98 to elicit reproductive history + individual deployment dates
- Validated self-reported outcomes against military hospitalization records

Results

- 3285 women had a pregnancy-related admission in a military hospital
- 1558 completed the questionnaire

Dates of delivery (or fetal loss), weeks of gestation, and individual deployment dates identified:

415 Gulf-war exposed pregnancies

298 GWV postwar conceptions

427 NDV conceptions

Results

- The prevalence of stillbirths, spontaneous abortions, ectopic pregnancies, and induced abortions were similar among GWV-exposed pregnancies and NDV conceptions.
- Spontaneous abortions were significantly higher among postwar GWV conceptions (22.8%) compared to NDV conceptions (9.1%, adjusted OR: 2.92, 95% CI: 1.9 – 4.6)
- Ectopic pregnancies were significantly higher higher among postwar GWV conceptions (10.7%) compared to NDV conceptions (1.4%, adjusted OR: 7.7, 95% CI: 3.0 - 20)

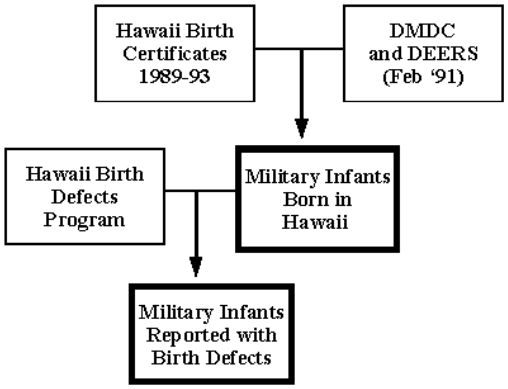
Conclusions

- Among women veterans who belonged to units that were deployed to the Gulf War:
- GWV-exposed conceptions and nondeployed conceptions had similar reproductive outcomes.
- However, GWV postwar conceptions were at increased risk for ectopic pregnancies and spontaneous abortions

Selection of Hawaii for Pilot Site

- **Large military population**
  - **20% of births have a military parent**
- **Same genetic referral site for military and civilian hospitals**
- **Parental SSN on birth certificate**
- **Military employment on birth certificate**

Military Infants Reported to the Hawaii Birth Defects Program



How to improve statistical power? How to reduce multiple comparisons?

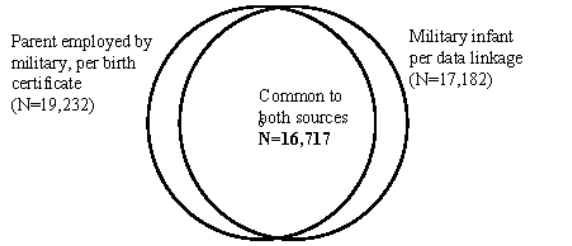
	GWV (n=4,956)	NDV (n=13,123)	RR (95%CI)
Tricuspid valve insufficiency**	10 (27)	10 (10)	2.6 (1.1 – 6.4)†
Aortic valve stenosis	5 (10)	2 (1.5)	6.6 (1.4 - 45)‡
Coarctation of aorta	5 (10)	3 (2)	4.4 (1.1 - 21)§

**per 10,000 live births, ** California births excluded,*

†p=0.023, ‡p=0.019, §p=0.04

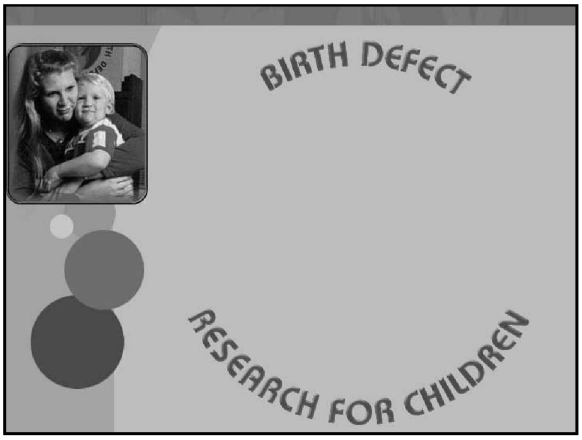
27 comparisons, expect 5% (1.4) to differ due to chance, observe differences in 3

Enumeration of Military Infants: Military Employment on Birth Certificate vs. Linkage Method, Live Births, Hawaii, 1989-93



Sensitivity = 87% **Specificity = 99%** **Positive Predictive Value = 97%**

Presentation 2 – Betty Mekdeci



National Birth Defect Registry

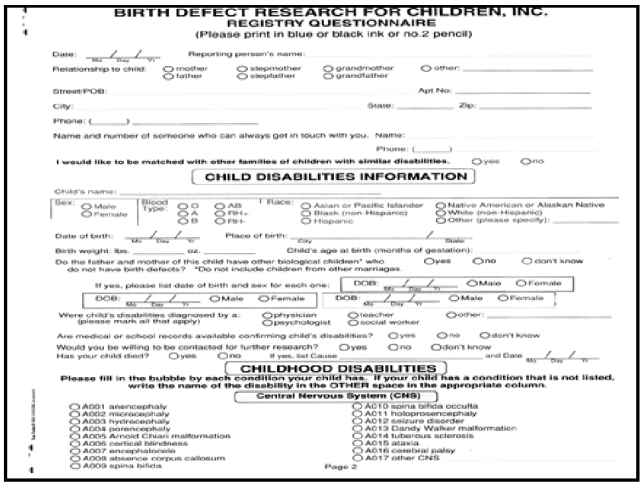
- Based on concept of "alert practitioner"
- Identifies patterns of birth defects with the same or similar exposures
- Collects data on maternal/paternal pre-conceptual and prenatal exposures
- Cases dually identified by individual symptoms and overall syndrome or category name
- Designed to raise hypotheses

Teratogens Identified by Alert Practitioners

- Thalidomide
- Rubella
- Dilantin
- DES
- Alcohol
- Methyl Mercury
- Radiation

Scientific Advisory Board

- Peter Kahn, Ph.D.
  Rutgers University
- James Murphy, Ph.D.
  University of Colorado
- Theo Colborn, Ph.D.
  World Wildlife Fund
- Stuart Newman, Ph.D.
  New York Medical College
- Shanna Swan, Ph.D.
  California Department of Health Services
- Maureen Paul, M.D.
  University of Massachusetts
- Wayland Swain, Ph.D.
  Eco Logic Company
- Janette Sherman, M.D.
  Wayne State University



BIRTH DEFECT RESEARCH FOR CHILDREN, INC.
REGISTRY QUESTIONNAIRE
(Please print in blue or black ink or no.2 pencil)

Date: Reporting person's name:

Relationship to child: mother stepmother grandmother other:
father stepfather grandfather

Street/POB: Apt No:

City: State: Zip:

Phone: ( )

Name and number of someone who can always get in touch with you. Name:

Phone: ( )

I would like to be matched with other families of children with similar disabilities. yes no

CHILD DISABILITIES INFORMATION

Child's name:

Sex: Male Female | Blood Type: O AB A Rh+ B Rh- | Race: Asian or Pacific Islander Native American or Alaskan Native Black (non-Hispanic) White (non-Hispanic) Hispanic Other (please specify):

Date of birth: Mo Day Yr Place of birth: City State

Birth weight: lbs. oz. Child's age at birth (months of gestation):

Do the father and mother of this child have other biological children* who do not have birth defects? *Do not include children from other marriages. yes no don't know

If yes, please list date of birth and sex for each one: DOB: Male Female

DOB: Male Female DOB: Male Female

Were child's disabilities diagnosed by a: (please mark all that apply) physician teacher other:
psychologist social worker

Are medical or school records available confirming child's disabilities? yes no don't know

Would you be willing to be contacted for further research? yes no don't know

Has your child died? yes no If yes, list Cause and Date

CHILDHOOD DISABILITIES

Please fill in the bubble by each condition your child has. If your child has a condition that is not listed, write the name of the disability in the OTHER space in the appropriate column.

Central Nervous System (CNS)

A001 anencephaly
A002 microcephaly
A003 hydrocephaly
A004 porencephaly
A005 Arnold Chiari malformation
A006 cortical blindness
A007 encephalocele
A008 absence corpus callosum
A009 spina bifida
A010 spina bifida occulta
A011 holoprosencephaly
A012 seizure disorder
A013 Dandy Walker malformation
A014 tuberous sclerosis
A015 ataxia
A016 cerebral palsy
A017 other CNS

Page 2

Registry Projects

- Bendectin
- Agent Orange
- Gulf War
- Community based
  - Dickson, TN - oral cleft cluster

Dickson Cleft Palate Investigation

- 19 cases of cleft palate/2 expected
- TCE leachate from old landfill
- Toluene emissions from printing company
- Excessive Trihalomethanes in water
- CDC confirmed cluster
- EPA contracted new report on landfill
- Landfill now capped
- Tennessee legislature voted to move source of community's water to a different river

Gulf War Exposures

- DEET
- Permethrin
- Pyridostigmine
- Pentachlorophenol
- Benzocaine sulfur
- Aluminum phospide
- Baygon
- Boric Acid
- Sevin
- Amidinohydrazone
- Diazinon
- Dursban
- Dichlorvos
- Ficam
- Carbaryl
- Lindane
- Malathion
- Oil Well Fires
- Leaded fuels
- Depleted Uranium
- Solvents
- Decontam agent
- Malaria Pills
- Campfires
- Leishmaniasis
- Chemical warfare agents
- CARC
- Vaccinations
- D-phenothrin
- Allethrin
- Paint
- Others

Disability Frequency

• Resp. Infect.	117	• VSD	35
• Ear Infect.	92	• Drug Reaction	34
• Motor Delay	86	• Hypotonia	34
• Colic as Baby	62	• Seizures	33
• Speech	62	• Acne-like Rash	33
• Allergies	57	• Thrush	32
• Jaundice	56	• Mood Swings	32
• Reflux	52	• Pneumonia	29
• Heart Murmur	51	• Birth Mark	28
• High Fevers	46	• Stomach problems	28
• Ext. Ears	40	• Sleep disorder	26
• Asthma	38	• Walks on tiptoes	26
• Food Sens.	38	• Goldenhar	26
• Eczema	35	• Up. Limb Reduction	25

Male-Mediated Birth Defects

Evidence from Experimental and Epidemiological Studies

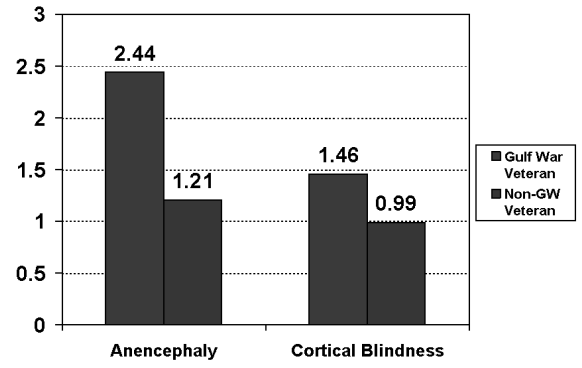
- Toluene
- Benzene
- Lead/mercury
- Trichloroethane
- Solvents
- Dyes
- Cigarette smoke/alcohol
- Drugs

Possible Outcomes

- Congenital malformations
- Spontaneous abortions
- Low birth weight
- Childhood cancers
- Developmental, neurobehavioral, neuroendocrine, neurochemical abnormalities

Birth Defect Research for Children, Inc.

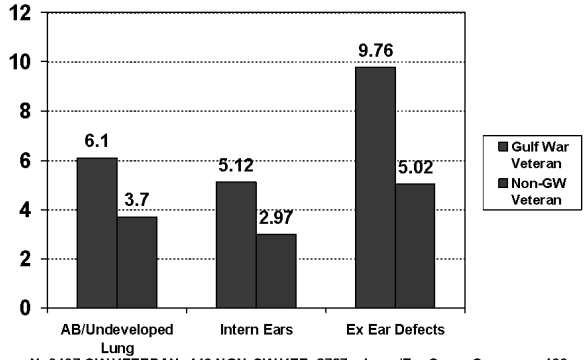
National Birth Defect Registry – Children of GW Vets/ Non-GW Vets



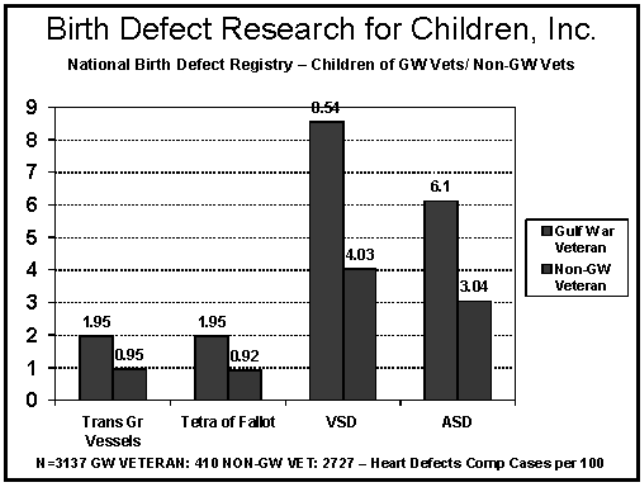
N=3137 GW VETERAN: 410 NON-GW VET: 2727 – CNS Comp Cases per 100

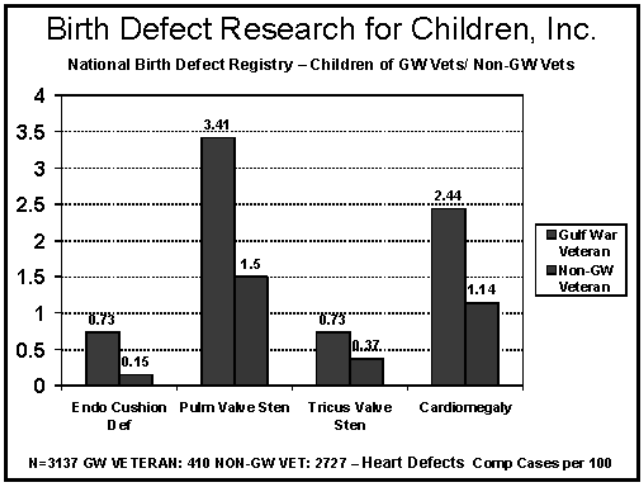
Birth Defect Research for Children, Inc.

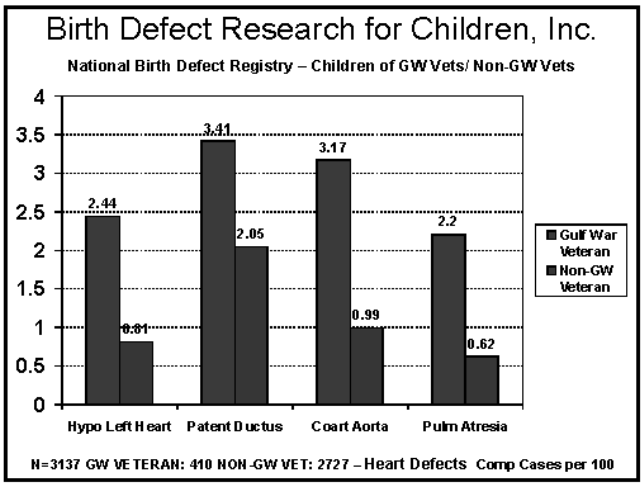
National Birth Defect Registry – Children of GW Vets/ Non-GW Vets

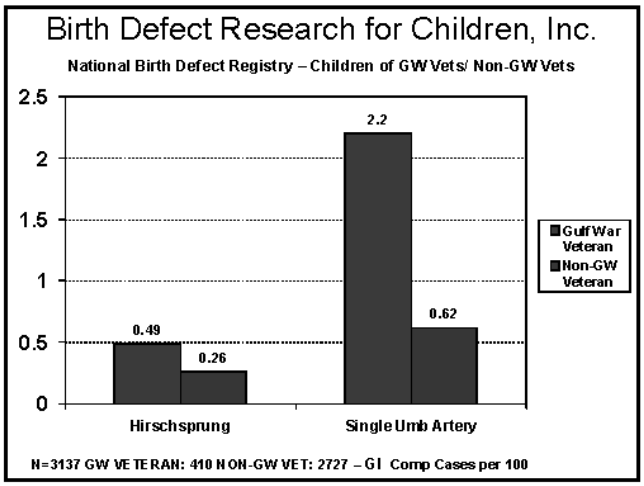


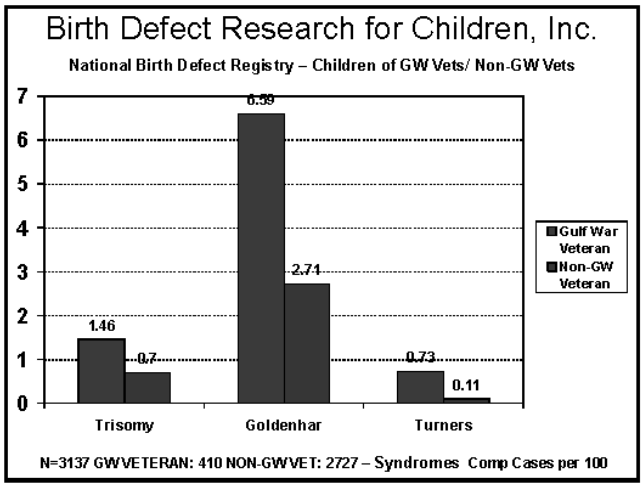
N=3137 GW VETERAN: 410 NON-GW VET: 2727 – Lung/Ear Comp Cases per 100

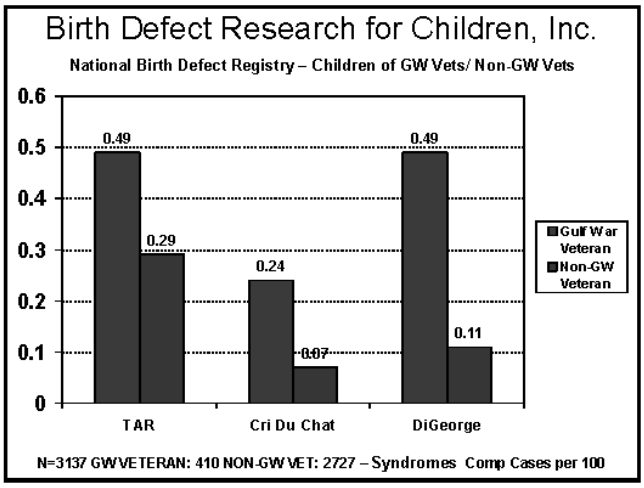

Birth Defect Research for Children, Inc.
National Birth Defect Registry – Children of GW Vets/ Non-GW Vets
9
8
7
6
5
4
3
2
1
0
1.95
0.95
1.95
0.92
8.54
4.03
6.1
3.04
Trans Gr Vessels
Tetra of Fallot
VSD
ASD
Gulf War Veteran
Non-GW Veteran
N=3137 GW VETERAN: 410 NON-GW VET: 2727 – Heart Defects Comp Cases per 100

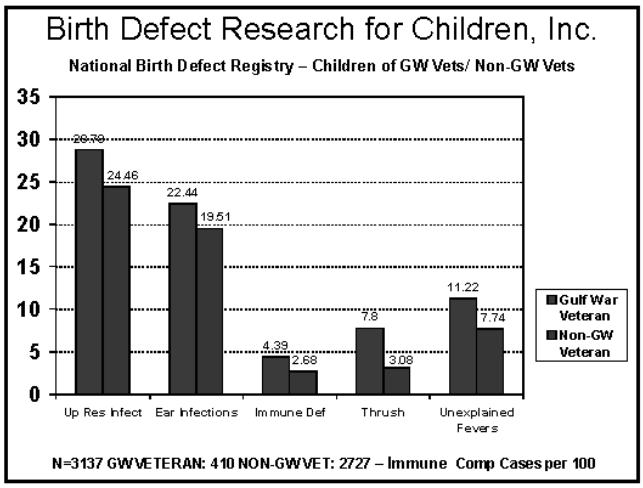

Birth Defect Research for Children, Inc.
National Birth Defect Registry – Children of GW Vets/ Non-GW Vets
4
3.5
3
2.5
2
1.5
1
0.5
0
0.73
0.15
3.41
1.5
0.73
0.37
2.44
1.14
Endo Cushion Def
Pulm Valve Sten
Tricus Valve Sten
Cardiomegaly
Gulf War Veteran
Non-GW Veteran
N=3137 GW VETERAN: 410 NON-GW VET: 2727 – Heart Defects Comp Cases per 100

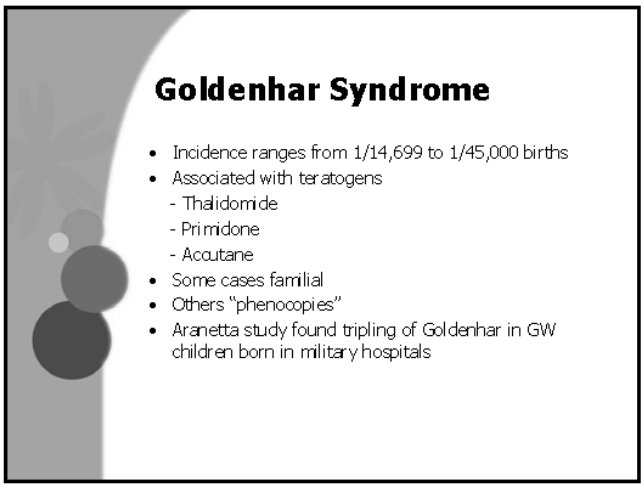

Birth Defect Research for Children, Inc.
National Birth Defect Registry – Children of GW Vets/ Non-GW Vets
4
3.5
3
2.5
2
1.5
1
0.5
0
2.44
0.81
3.41
2.05
3.17
0.99
2.2
0.62
Hypo Left Heart
Patent Ductus
Coart Aorta
Pulm Atresia
Gulf War Veteran
Non-GW Veteran
N=3137 GW VETERAN: 410 NON-GW VET: 2727 – Heart Defects Comp Cases per 100


Birth Defect Research for Children, Inc.
National Birth Defect Registry – Children of GW Vets/ Non-GW Vets
2.5
2
1.5
1
0.5
0
0.49
0.26
2.2
0.62
Hirschsprung
Single Umb Artery
Gulf War Veteran
Non-GW Veteran
N=3137 GW VETERAN: 410 NON-GW VET: 2727 – GI Comp Cases per 100


Birth Defect Research for Children, Inc.
National Birth Defect Registry – Children of GW Vets/ Non-GW Vets
7
6
5
4
3
2
1
0
1.46
0.7
6.39
2.71
0.73
0.11
Trisomy
Goldenhar
Turners
Gulf War Veteran
Non-GW Veteran
N=3137 GW VETERAN: 410 NON-GW VET: 2727 – Syndromes Comp Cases per 100


Birth Defect Research for Children, Inc.
National Birth Defect Registry – Children of GW Vets/ Non-GW Vets
0.6
0.5
0.4
0.3
0.2
0.1
0
0.49
0.29
0.24
0.07
0.49
0.11
TAR
Cri Du Chat
DiGeorge
Gulf War Veteran
Non-GW Veteran
N=3137 GW VETERAN: 410 NON-GW VET: 2727 – Syndromes Comp Cases per 100


Birth Defect Research for Children, Inc.
National Birth Defect Registry – Children of GW Vets/ Non-GW Vets
35
30
25
20
15
10
5
0
28.78
24.46
22.44
19.51
4.39
2.68
7.8
3.08
11.22
7.74
Up Res Infect
Ear Infections
Immune Def
Thrush
Unexplained Fevers
Gulf War Veteran
Non-GW Veteran
N=3137 GW VETERAN: 410 NON-GW VET: 2727 – Immune Comp Cases per 100


Goldenhar Syndrome
• Incidence ranges from 1/14,699 to 1/45,000 births
• Associated with teratogens
- Thalidomide
- Primidone
- Accutane
• Some cases familial
• Others "phenocopies"
• Aranetta study found tripling of Goldenhar in GW children born in military hospitals

Goldenhar Case Study

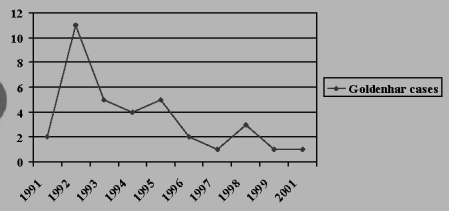
- 24 Goldenhar – fathers deployed
- 7 Goldenhar critera fathers deployed
- 2 Goldenhar fathers in Gulf after war
- 33 Goldenhar associated with Gulf service

Goldenhar Case Study

7 Goldenhar fathers non-deployed

23344	Steel worker
22970	Shots/solvents
26815	Cont gear
26896	Shots/Naptha
30868	Shots/lead fuel
45947	mechanic
48695	Cont gear

Goldenhar Case Study
DOB Distribution

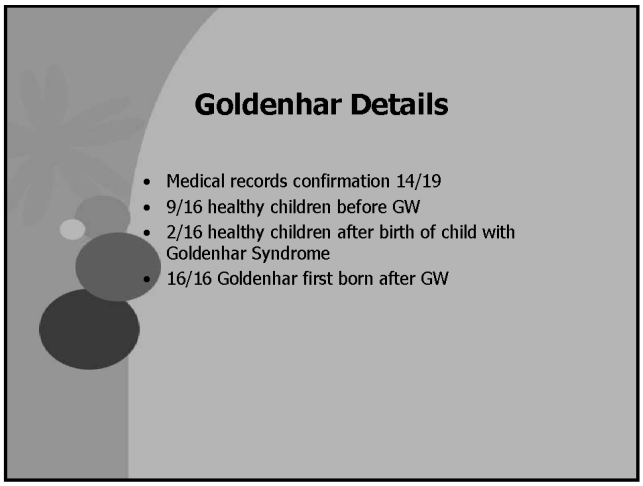


Goldenhar Case Rates

- 16 D Goldenhar DOB prior 10/1/93
- 3 ND Goldenhar DOB prior 10/1/93
- 56,782 births to deployed vets*
- 68,908 births to non-deployed vets*

Crude rates for Goldenhar:
Deployed – 28 per 100,000
Non-deployed – 4 per 100,000

*Araneta, Teratology, 1997.


Goldenhar Details
• Medical records confirmation 14/19
• 9/16 healthy children before GW
• 2/16 healthy children after birth of child with Goldenhar Syndrome
• 16/16 Goldenhar first born after GW

Presentation 3 – Han Kang

A Review of Medical Records for 206 Children with Birth Defects Reported by Gulf War Era Veteran Parents

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

Environmental Epidemiology Service
Department of Veterans Affairs

October 2003

Background

The National Health Survey of Gulf War Era Veterans and Their Families, Phase I & II, 1995-1996*

Unit Component	Male	Female	Total
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

* Kang et al, JOEM 2000; 421:491-501

SURVEY DESIGN

- Questionnaires through the mail
- Supplemental telephone interviews
- Physical examinations on a sample of veterans
- Validation through civilian, military and VA medical records

QUESTIONNARE INSTRUMENTS

- Limitations of activities
- Use of medical services (hospitalization, clinic visit)
- Chronic medical conditions (31 items)
- Prevalence of symptoms (48 items)
- Exposures in the Gulf theater (24 items)
- Prophylactics, vaccines (9 items)
- Reproductive health and pregnancy outcomes
  - live birth
  - birth defects
  - Infant death
  - still birth
  - miscarriage
- Life events (14 items)
- Smoking & drinking histories
- PTSD check list (PCL), 17 items

Percent Distribution of Selected Characteristics of Those Who Responded vs. Those Who Have Not Responded

Characteristics	Phase I Respondents (N=15,817)	Phase II Respondents (N=5,100)	Non Respondents (N=9,083)
Sex			
Male	79.3	81.8	80.3
Female	20.7	18.2	19.7
Age (Mean Age In 1991) Years	31.6	29.2	27.7
Race			
White	76.0	69.2	57.4
Black	16.4	24.2	32.8
Other	7.6	6.6	9.8
Marital Status			
Married	55.2	50.3	42.4
Single	39.4	44.7	53.5
Other	5.4	5.0	4.1
Rank			
Enlisted	82.6	88.0	92.4
Officer	15.8	11.0	7.0
Warrant	1.5	1.0	0.6

Percent Distribution of Selected Characteristics of Those Who Responded vs. Those Who Have Not Responded (cont'd)

Characteristics	Phase I Respondents (N=15,817)	Phase II Respondents (N=5,100)	Non Respondents (N=9,083)
Branch			
Air Force	12.9	12.8	8.6
Army	63.8	61.7	65.7
Marine	10.6	12.3	11.7
Navy	12.7	13.2	14.0
Unit Component			
Active	38.1	40.3	43.2
National Guard	27.8	26.7	24.7
Reserve	34.1	33.0	32.1
Current Active Duty			
Yes	20.3	16.2	-----
No	79.7	83.8	-----

Percent Distribution of Selected Characteristics of Those Who Responded vs. Those Who Have Not Responded by Gulf War Service Status

Characteristics	Gulf Veterans		Non-Gulf Veteran	
	Respondents (N=11,441)	Non-R † (N=3,559)	Respondents (N=9,476)	Non-R † (N=5,524)
Sex				
Male	81.4	80.0	78.1	80.5
Female	18.6	20.0	21.9	19.5
Age (Mean Age In 1991 Years	30.4	27.4	31.7	27.9
Race				
White	73.7	55.7	75.1	58.7
Black	19.0	34.1	17.4	31.8
Other	7.3	10.2	7.5	9.5
Marital Status ‡				
Married	52.5	42.9	55.5	42.1
Single	42.2	52.9	38.9	53.9
Other	5.3	4.2	5.5	4.0
Rank				
Enlisted	86.3	93.3	81.0	91.8
Officer	12.4	6.1	17.4	7.6
Warrant	1.3	0.6	1.5	0.6

Percent Distribution of Selected Characteristics of Those Who Responded vs. Those Who Have Not Responded by Gulf War Service Status (con't)

Characteristics	Gulf Veterans		Non-Gulf Veterans	
	Respondents (N=11,441)	Non-R † (N=3,559)	Respondents (N=9,476)	Non-R † (N=5,524)
Branch				
Air Force	12.5	8.4	13.4	8.7
Army	63.2	63.7	63.4	67.2
Marine	11.2	12.2	10.8	11.4
Navy	13.1	15.8	12.4	12.6
Unit Component				
Active	37.3	46.7	40.2	40.8
National Guard	28.3	23.3	26.5	25.7
Reserve	34.4	30.1	33.2	33.5
Current Active Duty				
Yes	19.2	-----	19.4	-----

† Non R= non-respondents
‡ Marital Status at the time of deployment

National Health Survey Phase I and II

Publications

- Kang HK, Mahan CM, Lee KY, Magee CA, Murphy FM. Illness among United States veterans of the GulfWar, a population based survey of 30,000 veterans. J Occup Environ Med 2000;42:491-501.
- Kang HK, Magee C, Mahan CM, Lee KY, Murphy FM, et al. Pregnancy outcomes among US GulfWar veterans: a population based survey of 30,000 veterans. Ann Epidemiology 2001;11:504-511
- Kang HK, Mahan CM, Lee KY, Murphy FM, et al. Evidence for a deployment related GulfWar syndrome by factor analysis. Archives Environmental Health 2002; 57:61-68
- Kang HK, Natelson BH, Mahan CM, Lee KY and Murphy FM. Post-traumatic stress disorder and chronic fatigue syndrome-like illness among GulfWar veterans: A population based survey of 30,000 veterans. Am J Epidemiol 2003;157:141-148 .
- Mahan CM, Kang HK, Dalager NA, et al. Anthrax vaccination and self-reported symptoms functional status, and medical conditions in the National Health Survey of Gulf War Era Veterans and Their Families. Ann Epidemiol 2003; 13:1-8
- Kang HK, Dalager NA, Ishii EK, et al. The role of sexual harassment and assault in PTSD among GulfWar veterans, manuscript submitted, under revision.

Table 1: Reported birth defects among index liveborn infants by Gulf deployment and gender of veterans

Birth Defects	Gulf (N= 2707) N	(%)	Non-Gulf (N= 2266) N	(%)	Adjusted OR(95%CI)
Likely defects					
Male	120	(5.4)	47	(2.8)	1.94(1.37-2.74)
Female	26	(5.5)	13	(2.3)	2.97(1.47-5.99)

Kang et al, Ann Epidemiol 2001; 11: 504-511

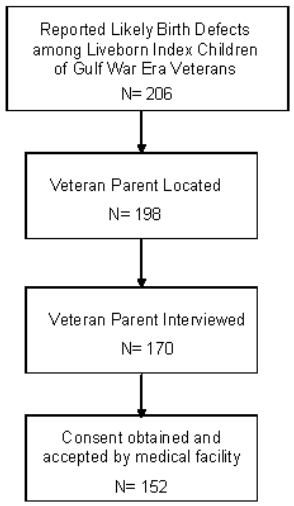


Fig. 1: Disposition of Medical Record Search

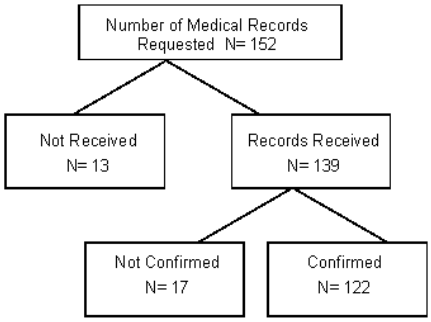


Fig. 2: Presence of Evidence Supporting Self-Reported Birth Defects in Medical Records

Table 2: Disposition of medical record review by parent Gulf War deployment status

Disposition	Gulf (N= 146)		Non-Gulf (N= 60)	
	N	%	N	%
Veteran Interviewed	126	86	44	73
Veteran Consented	112	(89)	40	(91)
Record Received	102	(91)	37	(93)
Male	83		25	
Female	19		12	
Self-Report Confirmed	87	(85)	35	(95)
Male	71		24	
Female	16		11	

Table 3: Confirmation rate by groups of birth defects and parental Gulf War deployment status

Group of Birth Defects	Gulf # Records	Gulf # Conf	Non-Gulf # Records	Non-Gulf # Conf
1. Chromosonmal Abnormality	5	5	0	0
2. Multiple Anomalies (Except Chromosomal & Heritable Genetic)	7	7	9	9
3. Isolated Anomaly	75	63	24	23
4. Congenital Malignancy	1	1	0	0
5. Heritable Genetic Disease	2	2	0	0
6. Undescribed Isolated Heart Abnormality	8	6	2	1
7. Other Poorly Described Defect (on-Cardiac)	4	3	2	2
Total	102	87	37	35

Table 4. Adjusted relative risk estimates for likely birth defects

Gender	Phase I & II	Adjusted relative risk(95% confidence interval) Green's method [a]	Direct [b]	Confirmed Cases [c]
Male veterans	1.98 (1.39-2.83)	2.78	1.72(1.21-2.43)	2.24(1.41-3.55)
Female veterans	2.53 (1.23-5.27)	2.71	2.26(1.12-4.56)	1.78(0.83-3.84)

[a] True risk ratio = [P1/P2 – (1 –Pred$_2$)]/Pred$_2$, where Pred$_2$ denotes the positive predictive value within the non-Gulf veteran group, as defined by Green: Kelsey, JL et al. 1986

[b] dRR = (self-report cases Gulf/# live birth Gulf) x confirmation rate Gulf ÷(self-report cases non-Gulf / # live birth non-Gulf) x confirmation rate non-Gulf

[c] cRR= (confirmed cases Gulf/# live birth Gulf) ÷ (Confirmed cases non-Gulf / # live birth non-Gulf)

Summary

- Among those veterans who were located, and who consented to release their medical records, reported birth defects were documented in medical records for 85% of Gulf War veterans' children and 95% of non-Gulf veterans' children.
- The association of the reported birth defects among children and veteran's military service in the Gulf War was supported by a review of medical records.

Presentation 4 – Lea Steele

Research Advisory Committee on Gulf War Veterans' Illnesses

Update on Published Research

Lea Steele, Ph.D.

Update on Published Research

- Medical/Physiological
  - ALS Studies
  - PON-1 levels
- Exposures
  - Review of effects of chemical warfare on Gulf veterans
  - DU
- Consensus statement on unexplained symptoms
- Health effects of Bosnia deployment

Update on Published Research Medical: ALS Studies

- Occurrence of ALS among Gulf War veterans
  R Horner et al, Neurology 2003: 742-9

  Identified 40 ALS cases in Gulf vets, 67 cases in nondeployed vets

  ALS in all Gulf War vs. era veterans: RR = 1.92 (1.29-1.82)
  Air Force veterans only: RR = 2.68 (1.24-5.78)

  Using self-reported deployment status
  ALS in Gulf War vs. era veterans: RR = 2.74 (1.87 – 4.01)
  Air Force veterans only: RR = 5.38 (2.67 – 10.85)

Update on Published Research Medical: ALS Studies

- Excess Incidence of ALS in Young Gulf War veterans
  R Haley, Neurology 2003:750-6

  Identified 20 ALS cases, 17 had onset before age 45
  No access to cases identified by VA re3cords and ALS Association

  Compared number of diagnosed ALS cases in Gulf vets to expected number (based on ALS mortality rates in U.S. males)

- Found:
  1991-1994: Number of Gulf veteran ALS cases similar to expected
  1995-1998: Ratio observed/expected = 2.27 (1.27 – 3.88)
  1998 only: Ratio observed/expected = 3.19 (1.03 – 7.43)

Update on Published Research Medical: Paraoxonase

- Paraoxonase in Persian Gulf War veterans
  Hotopf et al, J Occup Environ Med 2003:668-75
- Measured serum PON1 in:
  - healthy Gulf War veterans
  - symptomatic Gulf War veterans
  - symptomatic Bosnia veterans
  - symptomatic nondeployed veterans
- Found:
  - PON1 activity did not differ in healthy vs ill Gulf vets veterans
  - PON1 activity was lower in Gulf cohort than other 2 cohorts

Update on Published Research Exposures: Chemical Agents

- Chemical Warfare and the Gulf War: A Review of the Impact on Gulf Veterans' Health
  JR Riddle, M Brown, T Smith, EC Ritchie, KA Brix, J. Romano
  Military Medicine 2003: 606-13.

  Reviewed evidence that nerve agents had adverse effects on Gulf veterans' health:
  - No reports of chemical nerve agent detection during the war
  - No confirmation of symptoms consistent with nerve agent exposures during the war
  - No evidence that nerve agents were used during the war
  - Acute/limited exposures without immediate symptoms do not produce lasting health effects
  - No increase in postwar hospitalizations or disease mortality in Gulf War vets
  - "Belief in" exposure to chemical weapons associated with illness

CONCLUSIONS: "Chemical warfare-nerve agent exposure is a very unlikely cause of the postulated 'Gulf War syndrome' or any illness among Gulf War veterans."
More research needed to understand the adverse health effects that result from a belief in chemical weapon exposure.

Update on Published Research Exposures: DU

Estimate of Time Zero Lung Burden of DU in Persian Gulf War Veterans by the 24-hour urinary excretion and Exponential Decay Analysis
A Durakovic et al Military Medicine 2003 168: 600-5.

In 11 Gulf vets, used 24-hour urine levels of uranium isotopes to estimate DU levels veterans experienced at time of exposure

No mention of association of DU levels with health

Undiagnosed Illnesses and Radioactive Warfare
A. Durakovic Croatian Medical Journal 2003: 520-32

Reviews history of war-related radiological exposures and their impact on military and civilian populations

Update on Published Research: Consensus Statement

- Unexplained Symptoms After Terrorism and War: An Expert Consensus Statement
  D Clauw et al, J Occup Environ Med 2003: 1040-1048

  Expert panel found that divergent/overlapping unexplained symptoms occur after wars and terrorist acts

  The consensus development project resulted from the work of an international planning committee that included representatives of federal agencies, veterans' service organization, and academia

Update on Published Research: Consensus Statement

- Unexplained Symptoms After Terrorism and War: An Expert Consensus Statement
  D Clauw et al, J Occup Environ Med 2003:1040-1048.

  Focused on 3 questions:

  Q1. What is the strength of evidence that war/terrorism/catastrophes cause unexplained symptoms?
  A1.Consistent evidence

  Q2. What scientific evidence is needed to conclude that an exposed population is suffering from a unique illness?
  A2. New conditions rare, better to use existing case definitions for CFS, FMS

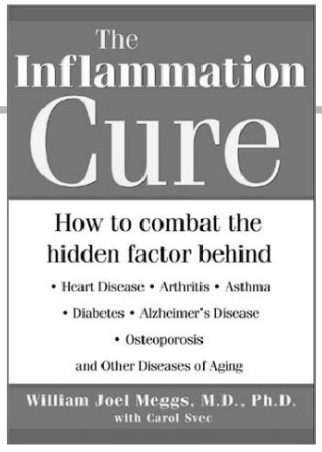
  Q3. What is evidence that postwar conditions can be prevented or mitigated?
  A3. Little research available. Additional research needed.

Update on Published Research: Health Effects of Bosnia Deployment

- The Health Effects of Peacekeeping (Bosnia, 1992-1996): a cross-sectional study--comparision with nondeployed military personnel
  Hotopf M, et al. Military Medicine 2003 168: 408-13.

  Comparison of health status and symptoms between U.K. Bosnia and nondeployed Bosnia-era veterans

- **Found:**
  - Bosnia veterans similar to nondeployed era veterans on almost all health measures
  - Bosnia veterans reported slightly better physical function than era veterans
  - Deployed veterans reported more heavy use of alcohol
  - Health of both groups generally good
  - Bosnia veterans who had also served in the Gulf War had significantly worse health outcomes than those who had not.



Presentation 5 – Carrolee Barlow

NTE and identification of possible molecular targets of neurotoxic exposures in Gulf War Veterans

Carrolee Barlow, M.D., Ph.D
Oct 27, 28 2003 Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses
US Department of Veteran Affairs

Drosophila *Swiss Cheese* (SWS) Gene

- Use information from model organisms.
- Progressive glial hyperwrapping and apoptosis of both neurons and glia.
- Mechanism unknown.

Environmental Toxins and Neurodegeneration

- Drosophila swiss cheese (*sws*)
- Biochemically identified Neuropathy Target Esterase (NTE) as the mammalian *sws (Glynn and others)*
- Thought to be targeted by a class of organophosphates (OPs) that cause progressive neurological symptoms

Chris Winrow

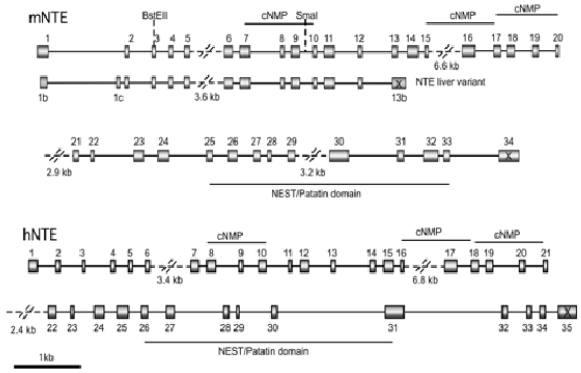
Neuropathy Target Esterase (NTE)

Esterase activity inhibited by a subset of organophosphates (OPs) responsible for neuropathies (paraoxan-resistant, mipafox sensitive).

Two functional domains identified:
- Regulatory N-terminal domain (cyclic nucleotide binding region/PKA regulatory subunit)
- Catalytic C-terminal domain (serine esterase)

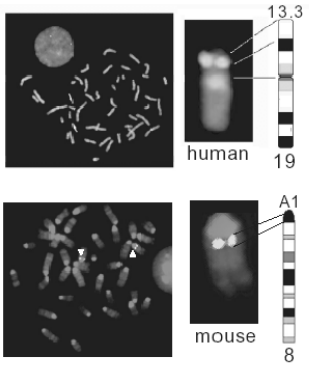
Natural substrate and function not clear.

NTE is highly conserved

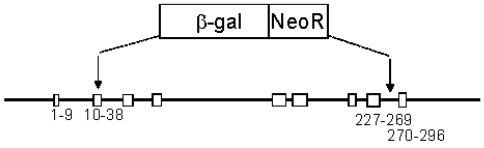


Human and Mouse NTE mapping

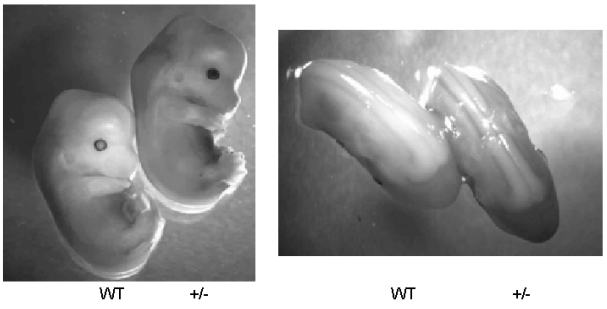
a

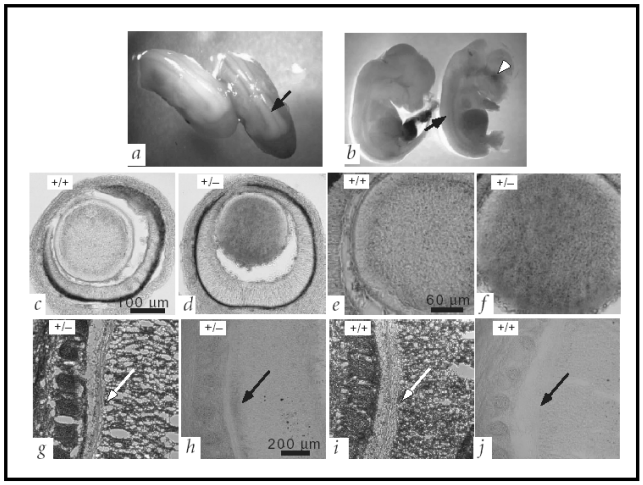


mNTE knock-out insertion sites

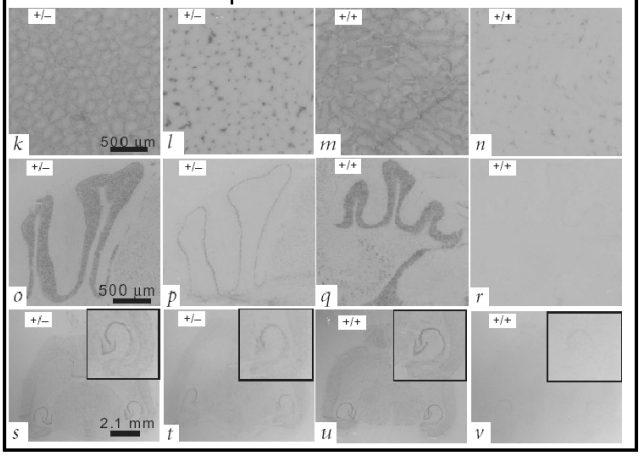


X-gal staining enables localization of NTE in heterozygous mice

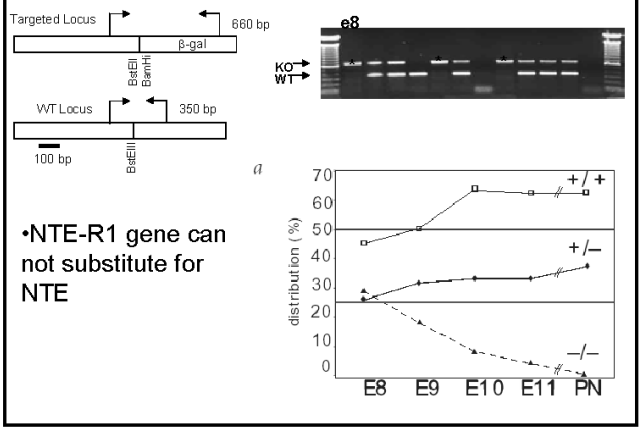




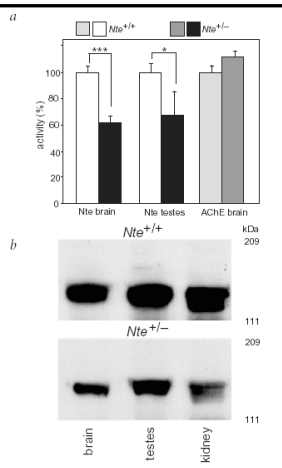
Expression in adult



NTE -/- Embryos Are Not Viable Beyond e8-e9



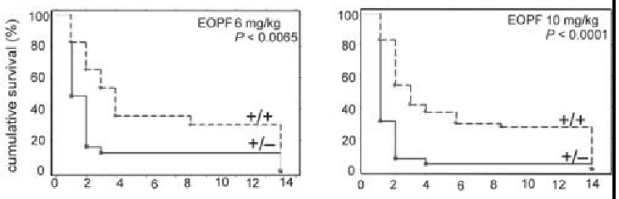
•NTE-R1 gene can not substitute for NTE



WT NTE heterozygous mice appear grossly normal but have reduced levels of NTE activity and protein compared to wildtype littermates (30-50%)

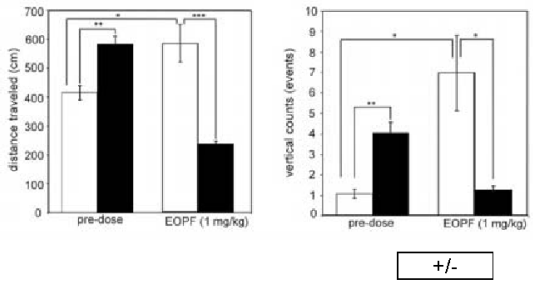
John Casida

Heterozygous mutants have +/- increased sensitivity to OPs WT.



Matt Hemming, Rob Helton

Partial inhibition of NTE (chemical OR genetic) leads to hyperactivity



Establishes that NTE is a target of OPs that cause neurological symptoms in mammals

news & views

Neurotoxic esterase: not so toxic?

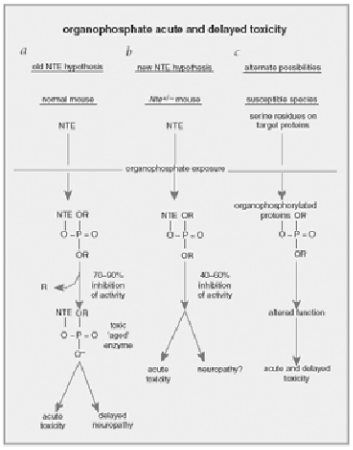
James P. O'Callaghan

Molecular Neurotoxicology Laboratory, Toxicology and Molecular Biology Branch, Health Effects Laboratory Division, Centers for Disease Control and Prevention–NIOSH, Morgantown, West Virginia 26505, USA. e-mail: jdc8@cdc.gov

Published online 17 March 2003; doi:10.1038/ntg1135

An altered form of an esterase has been implicated in the development of neurotoxicity after exposure to organophosphates. Mice deficient in this enzyme should be less susceptible to toxicity, but the opposite turns out to be the case.

Revisiting the NTE hypothesis. Pathways leading to acute toxicity and delayed neuropathy associated with exposure to organophosphates. According to a long-standing concept in neurotoxicology, the activity of a target esterase (neuropathy esterase or neuropathy target esterase) is inhibited by organophosphorylation at a key serine residue (refs. 4,5, 6). When inhibition of enzyme activity reaches 70–90% and, when phosphorylated NTE is modified by loss of a functional group (R), the enzyme is 'aged' and initiates the steps leading to delayed neuropathy and less prominent acute toxic effects. By generating *Nte*$^{+/-}$ mice, Winrow *et al.*[7] showed that mice with less NTE and lower activity of NTE are more sensitive to the toxic effects of prototypical organophosphate compounds (8), findings that seem to rule out the toxic gain-of-function (aged) phenotype that serves as the key feature of the NTE hypothesis. Alternative possibilities should be considered (2) because organophosphates have the potential to phosphorylate a variety of key serine-containing substrates, leading to altered function of a given protein[9,10] and potentially accounting for acute and delayed neurotoxic effects.



From O'Callahan News and Views

What next?

- Identify in vivo target of NTE
- Better define the biological function of NTE
- Identify individuals at risk?

Evidence that mouse brain neuropathy target esterase is a lysophospholipase

Gary B. Quistad*, Carrolee Barlow†, Christopher J. Winrow†, Susan E. Sparks*, and John E. Casida*‡

*Environmental Chemistry and Toxicology Laboratory, Department of Environmental Science, Policy, and Management, University of California, Berkeley, CA 94720-3112; and †Laboratory of Genetics, The Salk Institute for Biological Studies, 10010 North Torrey Pines Road, La Jolla, CA 92037

Contributed by John E. Casida, April 25, 2003

Table 1. Relationship between brain NTE-LysoPLA and NTE activities of NTE-deficient mice

Genotype*	NTE-LysoPLA, mAU/min†	NTE, AU†
Absolute activity		
+/+	4.09 ± 0.22	0.321 ± 0.018
+/−	2.43 ± 0.19‡	0.176 ± 0.045‡
Relative activity, %		
+/− ÷ +/+	59	55

Nte heterozygous 129S6/SvEvTac (*Nte*$^{+/-}$) transgenic mice and their wild-type littermates.
†NTE-LysoPLA and NTE assayed with lysolecithin and phenyl valerate, respectively, $n = 7$ for +/+ and 4 for +/− in each case as the average of four assays for NTE-LysoPLA and two for NTE. Data are mean ± SE.
‡Significant difference ($P < 0.01$) for both NTE-LysoPLA and NTE (comparison of +/+ with +/−).

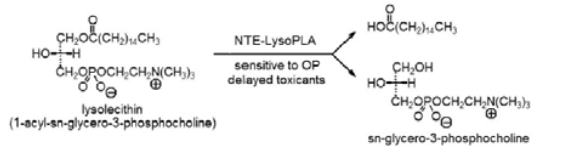


Fig. 2. Proposed biochemical lesion induced by OP delayed toxicants or neurotoxicants involving inhibition of NTE-LysoPLA, which normally hydrolyzes lysolecithin as its physiological substrate. The classical substrate for NTE is phenyl valerate, based on ease of assay (4, 12) rather than mechanistic considerations. NTE-LysoPLA and NTE in brain are resistant to paraoxon but sensitive to mipafox and other delayed toxicants or neurotoxicants.

7984 | www.pnas.org/cgi/doi/10.1073/pnas.1232473100 Quistad *et al.*

Table 2. Relationship between *in vivo* inhibition of brain NTE-LysoPLA and NTE activities and delayed toxicity

Toxicant and dose, mg/kg	Enzyme inhibition, %* NTE-LysoPLA	NTE	Delayed toxicity
EOPF			
1	18 ± 15	0 ± 0	–[†]
2	89 ± 12	89 ± 2	
3	100 ± 0	78 ± 5	+[†]
10	99 ± 1	95 ± 4	+[†]
(*S*)-octyl-BDPO			
5	71 ± 8	92 ± 7	+[†]
(*R*)-octyl-BDPO			
5	7 ± 8	6 ± 7	–[†]
o-Tolyloxy-BDPO			
3	20 ± 17	8 ± 4	–
10	70 ± 4	55 ± 13	–
30	89 ± 7	94 ± 7	–[‡]
100	87 ± 16	100 ± 0	–[‡]
DSF			
100	92 ± 9	100 ± 0	+
Tribufos			
30	7 ± 8	11 ± 9	–[§]
100	85 ± 16	100 ± 0	+[§]

Compounds were administered i.p. to Swiss–Webster mice with determinations of enzyme activities at 4 h and delayed toxicity at 3 days.
*NTE-LysoPLA and NTE were assayed with lysolecithin and phenyl valerate, respectively. $n = 3$ in each case as the average of duplicate assays for NTE-LysoPLA and single determinations for NTE. Data are mean ± SE.
[†]Ref. 14.
[‡]Cholinergic poisoning signs at 100, but not 30, mg/kg.
[§]Ref. 16.

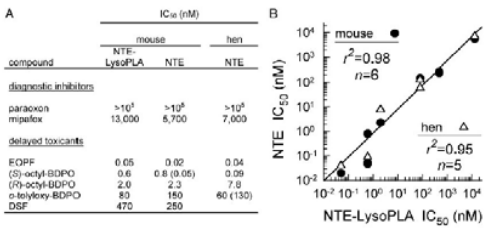
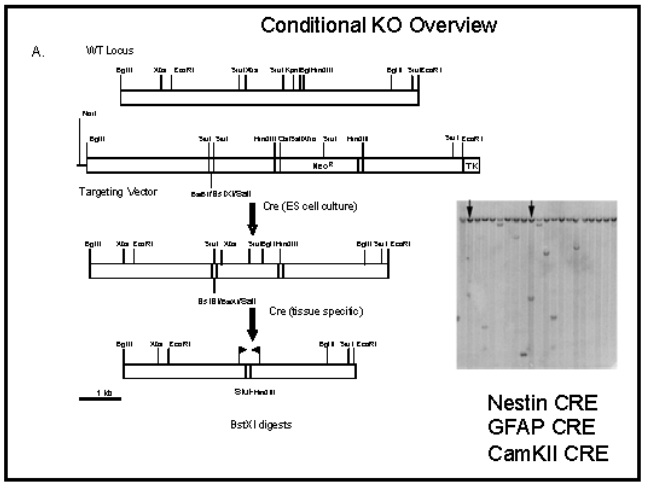


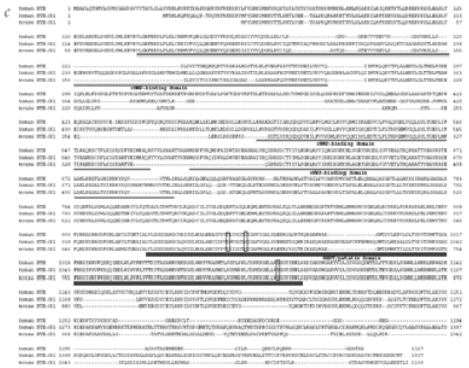
Fig. 3. Relationship between *in vitro* sensitivities of brain NTE-LysoPLA and NTE activities. NTE-LysoPLA and NTE were assayed with lysolecithin and phenyl valerate, respectively. Compound structures are shown in Fig. 1. (*A*) The data for mouse NTE-LysoPLA for all compounds and mouse NTE for paraoxon, (*S*)-octyl-BDPO, and DSF are from this study with Swiss–Webster mice. Other data for mouse NTE are from this laboratory (14, 16) or Veronesi *et al.* (26) for *o*-tolyloxy-BDPO. The hen NTE data are from Wu and Casida (13, 15, 27), Johnson (11), and Veronesi *et al.* (26). (*B*) Correlation for sensitivity of NTE-LysoPLA from mouse brain versus NTE from mouse brain (●) and hen brain (△). Correlation coefficients (r^2) do not include tabulated values for paraoxon (>10^3 nM) or those in parentheses, which were determined by a different investigator (0.05 nM for mouse NTE) or a different laboratory (130 nM for hen NTE).

Generate animals with tissue and time specific complete loss of NTE function



Use advancing genetic/genomic/protein technologies to define populations at increased risk if exposed to OP's

Highly conserved



High throughput genotyping services/products

- Perlegen
- Affymetrix

- Sequenom
- DeCode
- many others

Measuring levels in blood or skin biopsy samples

- Gene expression - Affymetrix
- or TaqMan based probes

- Best to evaluate protein level by Elisa or activity assays

Correlating biochemical and genetic markers with disease

- Clinical databases combining all types of data in high level analytical relational databases- Teradata (NCR)
- Information Management Consultants (IMC, McClain VA)
- Walter Reed/Windber/USUHS

Press Release Source: NCR Corporation

Data Warehousing Used for First Time to Create a Single Database to Help Find the Cause of Breast Cancer
Tuesday September 23, 11:31 am ET Windber Research Institute Determines Teradata as the Only Solution to Aggregate, Seamlessly Integrate and Mine Biological and Clinical Data

SEATTLE--(BUSINESS WIRE)--Sept. 23, 2003-- Windber Research Institute has chosen Teradata, a division of NCR Corporation (NYSE:NCR - News), to create the first and only central data warehouse where molecular and clinical information is being assembled and seamlessly integrated in a single data warehouse to help find the cause of breast and other forms of cancer.

Windber Research Institute (www.wriwindber.org) is an integrated research facility that has the unique ability to simultaneously examine the function of many genes and proteins related to reproductive cancers and heart disease. The Institute is a key component of a multi-institutional coalition consisting of the Clinical Breast Care Project at Walter Reed Army Medical Center, the Joyce Murtha Breast Care Center at the Windber Medical Center, and the Immunology Research Center at the Uniformed Services University of the Health Sciences in Bethesda, Maryland.


Chris Ames
Emily Annas
Mario Caceres
Cathy Chung
Todd Carter
Joa Del Rio
Sebastian Fuchs
Anthony Garcia
Jennifer Greenhall
Matt Hemming
Joel Laucher
Iiris Hovatti
Rob Helton
Mark Latronica
Mike McConnell
Peter Nakaji
Ling Ouyang
Dan Pankratz
Rickard Sandberg
John Scheel
Rick Tennant
Kai Treuner
Chris Winrow
Matt Zapala
John Casida
David Lockhart
NIMH Neurogenomics
Searle Scholar Program
V Foundation
Klingenstein Foundation
DOD - NTE
Teradata
iMC

Presentation 6 – Wilkie Wilson

Neurotoxins and Gulf War Illness: An Overview of VA's Research Enhancement Award Program (REAP)

- Research Enhancement Award Program
  - Promote and support groups of VA investigators in programs of exceptional quality
  - Train new investigators (William Troust, MD -PSY)
  - Support core facilities for multiple investigators
  - Support small innovative pilot projects to generate new and novel approaches to medical problems
  - Durham, NC station (4/1/2003-3/31/2008)

An Overview of VA's Research Enhancement Award Program (REAP)

- Principal Investigator:
  - Roger Madison, Ph.D., Research Career Scientist
- Co-Investigators:
  - Scott Moore, M.D., Ph.D. – Psychiatry
  - Christine Marx, M.D., M.A. – Psychiatry
  - Scott Swartzwelder, Ph.D. – Neuropsychology (Senior RCS)
  - Wilkie Wilson, Ph.D. Pharmacology (Senior RCS)
  - Ashok Shetty, Ph.D. Anatomy (Research Scientist)

Neurotoxins, Hyperexcitability and Gulf War Illness

- Persian Gulf War Syndrome; Haley et al., JAMA, 1997
  - Impaired cognition
  - Confusion; ataxia
  - Arthromyo-neuropathy; muscle & joint pain
  - Phobias, apraxia,
  - Fever, adenopathy
  - Weakness and incontinence
  - Increased incidence of ALS?; Haley, Neurol., 2003

Neurotoxins, Hyperexcitability and Gulf War Illness

- Evidence for neuronal injury/loss in Gulf War Illness
  - Proton magnetic resonance spectroscopy shows decreased functional neuronal mass in basal ganglia of GWI patients compared to normal controls; *Haley et al., Arch. Neurol., 2000*
  - Rat model of GWI involving exposure to low-doses of: pyridostigmine bromide; N,N-diethyl m-toluamide (DEET); or permethrin demonstrates neuronal cell death in numerous brain regions; *Abdel-Rahman, Shetty, and Abou-Donia, Neurobiol. Disease, 2002, 10(3), 306-326; Exp. Neurol., 2001, 172(1), 153-171*

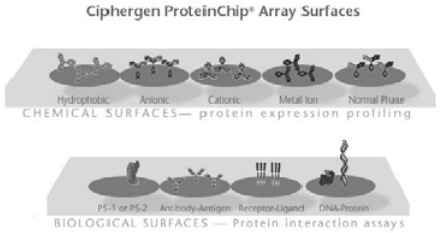
Neurotoxins, Hyperexcitability and Gulf War Illness

- Neurotoxins can lead to neuronal death due to hyperexcitability
  - Neurotoxins can cause local epileptiform discharges
  - Epileptiform activity can cause neuronal death
  - Even "neuroprotective" drugs may produce local hyperexcitability and be neurotoxic---memantine
- Therefore there may be a link between neurotoxins, neuronal hyperexcitability, and Gulf War Illness as well as other neurodegenerative diseases
  - Nerve injury, seizures, neuropsychiatric disorders

Durham VA REAP

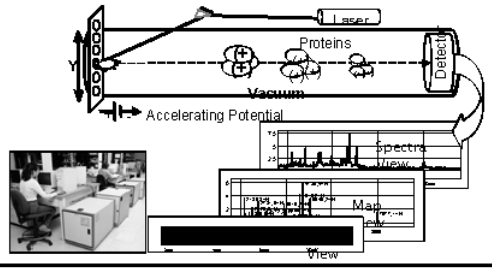
- Gene and protein expression in animal models of neuronal hyperexcitability and neurotoxin exposure
- Interested in brain sub-regions; e.g. hippocampus, basal ganglia, amygdala
  - Increase signal to noise if just the sub-region of interest can be analyzed separately from the rest of the brain
  - Requires technology that can work with small samples
- REAP support of the developing Proteomics Core Resource for the Durham, NC VAMC utilizing the Ciphergen Protein Chip instrument

Neurotoxins, Hyperexcitability and Gulf War Illness: Protein Chip Instrument



Neurotoxins, Hyperexcitability and Gulf War Illness: Protein Chip Instrument

TOF-MS Detection of Proteins Captured on ProteinChip®



Neurotoxins, Hyperexcitability and Gulf War Illness: Protein Chip Instrument

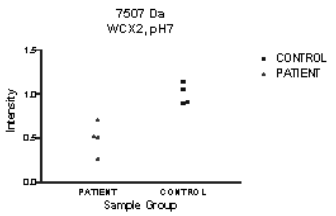
Serum Biomarkers in Schizophrenia

- Objective
  - To demonstrate the utility of ProteinChip®-SELDI-TOF technology for rapid screen of serum biomarkers in Schizophrenia patients
    - Differential biomarkers between patients and control;
    - Differential protein expression within patient or control population
- Materials
  - (small!)~100 ul frozen serum samples: 4 patient, 4 control
  - WCX2, SAX2, IMAC-Cu, H4 ProteinChip® arrays.

Neurotoxins, Hyperexcitability and Gulf War Illness: Protein Chip Instrument

Serum Biomarkers in Schizophrenia vs. Controls

M/Z	p
7507	0.0288
7958	0.0288
10288	0.0288
5228	0.0288
4648	0.0288
4253	0.0288
3884	0.0288
4121	0.0288



Neurotoxins, Hyperexcitability and Gulf War Illness: Amygdala and psychiatric disorders

- The amygdala is critical for conditioned fear (a model of PTSD and phobias)
- Amygdala lesions impair acquisition and expression of conditioned fear
- Partial amygdala kindling produces exaggerated fear and aggression
- Amygdala hyperexcitability has been proposed as a model of anxiety disorders

Neurotoxins, Hyperexcitability and Gulf War Illness: Amygdala and psychiatric disorders

- The amygdala has one of the lowest thresholds of any brain region for kindling and epileptiform activity
- Amygdala hyperexcitability may be produced by electrical stimulation, toxic agents, or stress.
- Maintenance of these forms of aberrant synaptic function ultimately depend on gene induction and new protein synthesis

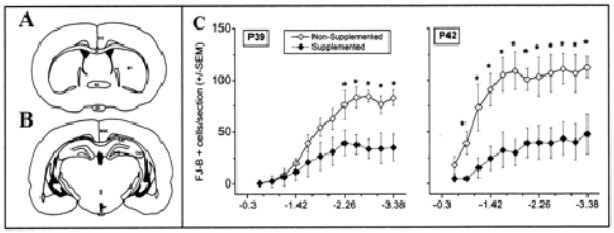
Neurotoxins, Hyperexcitability and Gulf War Illness: Amygdala and psychiatric disorders

- Proposed Pilot Study
  - Develop an *in vitro* model of psychopathology in a rodent brain slice preparation
  - Using multiple approaches, induce altered excitability in the amygdala
  - Perform microarray analysis of gene expression and SELDI/MS protein characterization to characterize specific biomarkers associated with the hyperexcitable amygdala network

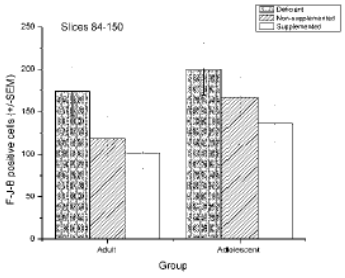
Neurotoxins, Hyperexcitability and Gulf War Illness: Neuroprotection by dietary choline

- Choline is a required dietary nutrient
- Required for neuronal integrity and synaptic transmission (acetylcholine)
- Agonist at nicotinic alpha-7 receptors
- Prenatal supplementation with choline provides neuroprotection
- Some evidence that adults are protected by choline supplementation

Prenatal choline supplementation is neuroprotective



Is postnatal choline supplementation neuroprotective?



Neurotoxins, Hyperexcitability and Gulf War Illness: Neuroprotection by dietary choline

Goals:

- Effects of dietary choline levels on neuronal excitability
- Effects on alpha-7 receptor function (alpha-7 desensitization?)
- Does adult supplementation provide neuroprotection?

Neurotoxins, Hyperexcitability and Gulf War Illness: Alcohol Exposure

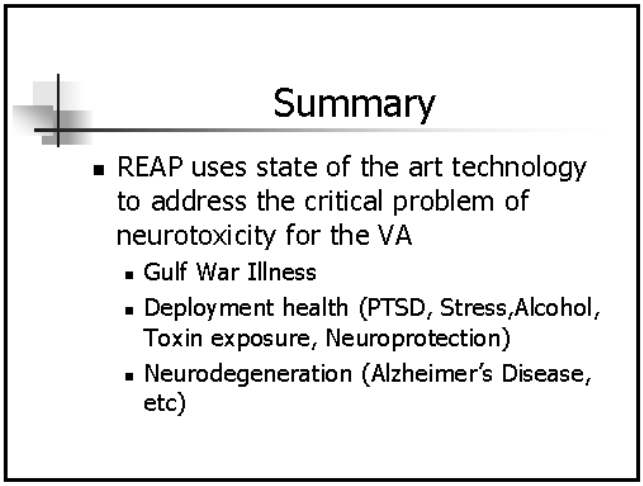
- The hippocampus is critical for learning and memory
- The hippocampus is damaged by repeated heavy exposures to alcohol
- One mechanism of this vulnerability is neuronal hyperexcitability

Neurotoxins, Hyperexcitability and Gulf War Illness: Alcohol Exposure

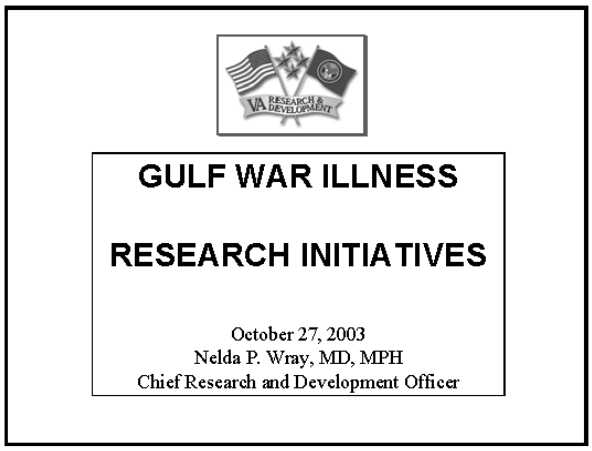
- Cholinesterase Inhibitors May Decrease Brain Choline Availability
  - AChE activity promotes brain choline availability
  - Blocking AChE action may decrease brain choline levels resulting in increased vulnerability to excitotoxicty in the brain.

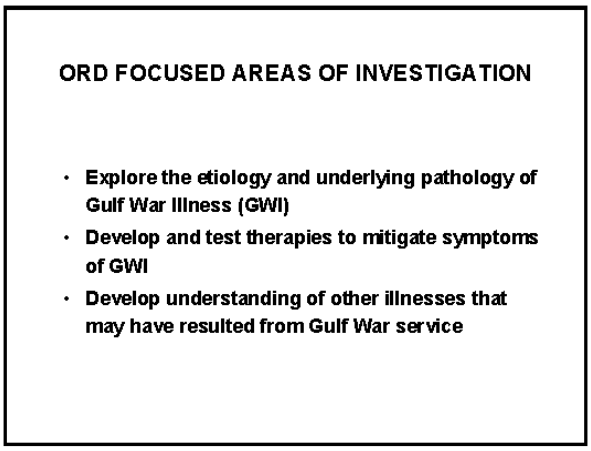
Neurotoxins, Hyperexcitability and Gulf War Illness: Alcohol Exposure

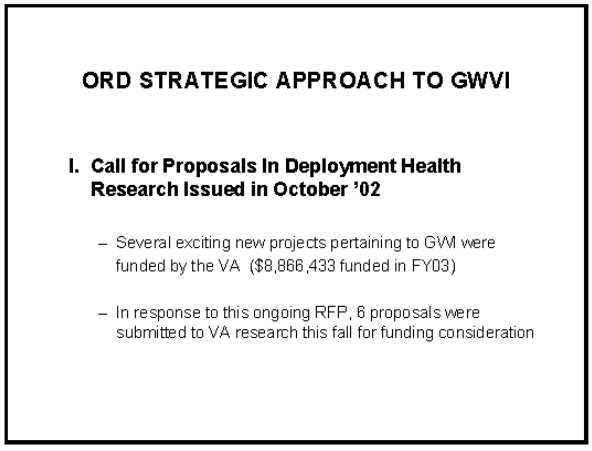
- Proposed Pilot Study
  - Assess alcohol-induced neurotoxicity in animals undergoing pharmacological exposure to anticholinesterase drugs.
  - Determine if dietary choline supplementation attenuates alcohol-induced neurotoxicity under these circumstances


Summary
REAP uses state of the art technology to address the critical problem of neurotoxicity for the VA
Gulf War Illness
Deployment health (PTSD, Stress,Alcohol, Toxin exposure, Neuroprotection)
Neurodegeneration (Alzheimer's Disease, etc)

Presentation 7 – Nelda Wray







ORD STRATEGIC APPROACH TO GWVI

III. ORD to Reorganize Gulf War Research Office

- Hiring of new scientific staff
- New staff will work with the RAC to catalog VA and non-VA research in Gulf War Illness
- New staff will proactively seek out research aimed at enhancing diagnosis, treatment and delineation of GWVI mechanisms

ORD STRATEGIC APPROACH TO GWVI

- **Understanding the etiology and underlying pathogenesis of GWI will lead to effective treatments**
- **VA research is focusing on**
  - Abnormalities of cholinergic neurotransmission
  - Neuroendocrine abnormalities
  - Neuroimaging techniques

ABNORMALITIES OF CHOLINERGIC NEUROTRANSMISSION

- **Documented exposures to anti-AChE agents in the Gulf War**
  - Pyriodostigmine bromide treatment
- **Abnormal AChE activity in animal model**
  - May lead to a depletion in cholinergic neurotransmitters producing symptoms such as memory loss and fatigue

ACETYLCHOLINESTERASE DYSFUNCTION

- **Neurochemical and Neurobehavioral Impact of Pyridostigmine Bromide Treatment**
  - East Orange VAMC (Funding for 5 years: $1,113,800)
  - Study will determine the nature and functional significance of reduced acetylcholinesterase (AChE) activity in the brain of rodents when administered pyridostigmine bromide (PB) under conditions of intense stress

ACETYLCHOLINESTERASE DYSFUNCTION

- **Acetylcholinesterase Activity in Gulf War Deployed and Era Veterans**
  - Iowa City VAMC (Funding for 2 years: $150,000)
  - Dr. Brad Doebbeling at the Iowa City VAMC and Dr. Soreq of Hebrew University will collaborate on a research study based on Dr. Soreq's preliminary findings that pyridostigmine bromide may have lead to chronic abnormalities in neurotransmitter systems and may be a cause of symptoms of illnesses in some Gulf War veterans

ACETYLCHOLINESTERASE DYSFUNCTION

- **Differential Gene Expression in Pathologies Associated with: Links to Gulf War Illness**
  - Durham VAMC (Funding for 6 years: $1,375,000)
  - This project will study differential gene expression in pathologies associated with 'neuronal hyper excitability'
  - This condition may be linked to pathologies associated with exposure to acetylcholinesterase inhibitors, such as organophosphates and carbamates (e.g., pyridostigmine bromide), potentially implicated in Gulf War illnesses

NEUROENDOCRINE DYSFUNCTION

- **Hypothalamic-Pituitary-Adrenal Axis Alterations in Gulf War and Vietnam Veterans**
  - Bronx VAMC (Funding for 4 years: $347,400)
  - This study will explore the hypothesis that ACTH levels may be reduced in patients with GWVI, which could reflect inhibition of the HPA axis or enhanced negative feedback
  - Elevated cortisol levels are associated with a number of diseases of the nervous system, such as memory disorders, and can be toxic to the hippocampus

NEUROIMAGING

- **State-of-the-art diagnostic techniques**
- **Assess brain function as well as brain structures**
- **Potentially will be key in assessing the underlying pathology of neurological problems in GW**

NEUROIMAGING

- **Effects of Gulf War Illnesses on Brain Structure and Function (Pilot Study)**
  - San Francisco VAMC (currently undergoing Merit Review)
  - Neuroimaging study proposed to examine structural changes in basal ganglia and pons of healthy and ill Gulf War Veterans
  - This pilot project will attempt to confirm previous findings in a much larger population
  - Two recent manuscripts suggest a relationship between central nervous system abnormalities seen in GWI and ALS, and this pilot will also investigate this issue

NEUROIMAGING

- **Neuroimaging Resource Centers RFP**
  - Neuroimaging Center -$1,000,000, Future Consortia - $5,000,000
  - Goal: Establishment of a coordinating center to guide efforts in developing, validating & standardizing neuroimaging research methodologies and metrics for GWVI
  - Development of consortia of sites

UNDERSTANDING OTHER ILLNESSES THAT RESULT FROM GULF WAR EXPOSURE

- **ALS**
  - Epidemiology of ALS
  - Mechanisms of injury due to ALS
  - Treatment for ALS

ALS

- **Mechanisms of Injury**
  - **The Role of Oxidative Injury in Spongiform Neurodegeneration**
    - Funding: $171,420, FY' 03
    - Using a rat model, this VA investigator aims to determine the pathogenic mechanism by which free radicals produce spongiform vacuolation and degeneration of neurons that result in a progressive neurodegenerative disorder

ALS

- **Mechanisms of Injury (continued)**
  - **Early Gene Triggers of Neurodegeneration**
  - Funding: $163,963, FY'03
  - VA is investigating the hypothesis that thrombin signaling, which may have neuroprotective effects, is recapitulated in neurodegenerative diseases involving neuronal cell death; the outcome of this study may be a new treatment strategy.

ALS

- **Treatment**
  - **Clinical Trials: Treating the primary disease**
    - **Clinical Trials – Albuterol to increase muscle mass**
    - Dr. Robert Ferrante, Bedford VAMC and colleges have published an article (Science Oct 3, 2003, Wild-Type Nonneuronal Cells Extend Survival of Superoxide Dysmutase deficient (SOD1) Mutant Motor Neurons in ALS Mice).
    - This study shows that nonneuronal cells that do not express mutant superoxide dysmutase delay degeneration and significantly extend survival of abnormal motor neurons.

ALS

- **Clinical Trials: Treating the primary disease (continued)**
  - **Clinical Trials – Gingko Biloba (Antioxidant)**
  - Dr. Robert Ferrante, Bedford VAMC
  - The SOD system is an intracellular enzymatic system that protects against oxidative stress which can lead to neuronal death. Animals with an abnormality in this protective mechanism develop a disease very similar to ALS, and serve as a model for studying the disease. Dr. Robert Ferrante is also studying many antioxidant agents in the mouse (superoxide dysmutase) model. VA has recently patented and licensed a Gingko Biloba treatment for ALS. Phase 1 trial will begin in 2004.

ALS

- **Clinical Trials: Treating the Complications**
  - **Dysphagia Research, Madison VAMC**
    - Some therapeutic trials are geared toward increasing muscle mass (reversing sarcopenia) through focused exercise.
    - In a study conducted at the Madison VAMC, muscles involved in the swallowing process are strengthened. MRI imaging has shown an increase in muscle mass, and clinical responses have been encouraging in terms of more effective swallowing and decreased aspiration.

ALS

- Clinical Trials: Treating the Complications **(continued)**
  - **A Phase II Study: Escalating Dose Response Trial of Tamoxifen Therapy on Mean Percent Predicted Isometric Strength in ALS, Madison VAMC**
  - Dr Benjamin Brooks, a VA Madison neurologist and researcher, is studying the impact of adding medications such as albuterol (known for increasing muscle mass in animals and humans) and tamoxifen (theoretically because of its testosterone effects) to exercise to reverse sarcopenia and increase functional strength.

OTHER POST-DEPLOYMENT HEALTH RESEARCH INITIATIVES

- Combat Trauma
  - **Prazosin Treatment for Combat Trauma PTSD Nightmares and Sleep Disturbance, Seattle VAMC (Funded for 5 years:$582,000)**
  - This placebo-controlled trial investigates possible mechanisms involving alpha-1 adrenergic receptor-mediated effects on sleep physiology, corticotropin releasing hormone secretion, and disruption of cognitive processing.

OTHER POST-DEPLOYMENT HEALTH RESEARCH INITIATIVES

- Parkinson's Disease
  - **Examining Possible Associations between Military Service during the Vietnam Era and Parkinson's Disease: A Feasibility Study, West Haven VAMC & Houston VAMC (Possible Funding for 1 year: $235,296)**
  - This one-year initiative determines the feasibility and design of an epidemiologic investigation examining the link between service in Vietnam and risk of Parkinson's Disease (PD).

OTHER POST-DEPLOYMENT HEALTH RESEARCH INITIATIVES

- Pre and Post Deployment Study
  - **Prospective Assessment of Neurocognition in Future Gulf-Deployed and Gulf-Non Deployed Military Personnel, New Orleans VAMC (This study will be funded by DoD for 2 years at $495,140 and by VA for 2 years at $55,700)**
  - The VA and the Department of Defense (DoD) are jointly funding a first-of its-kind study to ascertain whether or not deployment can lead to a deterioration in military service members' ability to function normally.

OTHER POST-DEPLOYMENT HEALTH RESEARCH INITIATIVES

- PTSD in Women
  - **A Randomized Clinical Trial for Cognitive-Behavioral Treatment for PTSD in Women, White River Junction VAMC**
  - VA investigators are examining differences between a "Prolonged Exposure" therapy and a "Present-Centered Therapy" at 3 months post treatment for post traumatic stress disorder.

ORD'S COMMITMENT TO GWVI

- ORD is dedicated to furthering the knowledge to understand GWI and its health consequences, and to develop effective treatments
- ORD is also dedicated to working closely with the Gulf War Veterans' Illnesses Research Advisory Committee to achieve our common goal

VA RESEARCH & DEVELOPMENT

Today's VA Research,
Leading Tomorrow's Health Care

Presentation 8 – Heremona Soreq and Steven Berkowitz

Serum enzyme activities in Gulf War Era Deployed Veterans and demographic parameters:

Progress report and comparison to healthy individuals

Keren Ailon, B.A. Ella H. Sklan, M.Sc., Boris Bryk, M.Sc
and Hermona Soreq, Ph.D.

The Hebrew University of Jerusalem

December, 2003

Objective

To determine serum enzyme activities among an anonymous group of Gulf War Veterans as compared to healthy U.S individuals.

AChE-R: The Stress Response Culprit

Long-term dangers

- Extracellular Impairment of cholinergic homeostasis
- (Kaufer, Nature, 98)

⇨ Depression

- Disruption of synaptic interactions
- (Soreq, Nature Neur, 01)

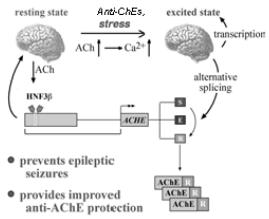
⇨ Cognitive deterioration

- Extrasynaptic functioning
- (Meshorer, Science, 02)

⇨ Hypersensitivity

- Intracellular induction of stress signal transduction
- (Birikh/Sklan, PNAS, 03)

⇨ Extended conflict behavior

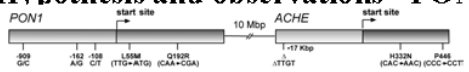


Symptoms associated with Multiple Syndromes

Hypothesis and observations - AChE

- Acetylcholinesterase (AChE) overproduction reflects organismal response to stressful stimuli or anti- AChE exposure [Kaufer et al., Nature 1998; Meshorer et al., Science 2002].
- In Healthy U.S individuals, demographic parameters were assessed and a series of equations developed in Jerusalem to predict serum enzyme levels [Sklan et al., submitted].
- In Gulf War Veterans, we observe conspicuous deviations from the predicted values.

Hypothesis and observations - PON



- Paraoxonase (PON) protects serum proteins (AChE included) from oxidative stress. In healthy individuals, we found an inverse correlation of AChE & PON with anxiety measures [Sklan et al.,submitted; Bryk et al., in preparation].
- Therefore, we further tested serum PON activities and examined their correlation to the AChE values.

Hypothesis and observations– Control enzyme assays

- Butyrylcholinesterase (BChE) is homologous to AChE. In both US and Israeli healthy individuals, AChE and BChE activities are directly correlated. We observe a different Correlation to AChE in Gulf War Veterans.
- Arylesterase (Aryl) activity reflects a distinct enzymatic activity of the PON protein (which differs from its paraoxon hydrolysing activity). Each of these activities distinctly depends on the genotype.
  In healthy individuals, Aryl activities are considerably less variable than PON activities.

Technical considerations

- The vast majority of the samples were from Caucasian males. Therefore, we excluded the other samples from most of our current data management (and used only Caucasian male samples from the healthy populations for comparison).
- Most psychoactive drugs may be expected to inhibit AChE activity and induce a feedback response of AChE overproduction, while suppressing liver metabolism and reducing PON and BChE activities.

Conclusions

- Gulf War Veterans display massive AChE overproduction.
- Deviations from the equation developed for healthy individuals calls for comparative genotype study to explore inherited origin for the discovered differences.
- Serum enzyme activities among Gulf War Veterans differ from those of healthy individuals in U.S. and Israel by several criteria.
- Genotype information will be required to develop serum PON activities, as surrogate measure of symptoms.

Conclusions – Control enzyme assays

- AChE and BChE activities are directly correlated both in Gulf War veterans and in healthy individuals. This correlation is less pronounced when BMI or age considerations are made , attributing much of the inter-individual variability to weight and age origins.
- In Gulf War veterans, Arylesterase activities show direct and significant correlation to BMI.

Acetylcholinesterase (AChE) Activity in Gulf War Deployed and Era Veterans

Bradley Doebbeling, M.D., M.Sc. and
Hermona Soreq, Ph.D.

Steven M. Berkowitz, Ph.D, Assistant Director
Cooperative Studies Program
VA Office of Research & Development

Background

- Approx. 700,000 US troops were deployed to the Gulf during Operation Desert Shield/Desert Storm
- Numerous deployed veterans reported multiple illness symptoms, (unexplained fatigue, pain, reduced cognitive function, and other symptoms)
- There is a great need to discover a biological mechanism or cause, in order to identify effective treatments for our veterans affected by GWVI

Neurotransmitters

- Acetylcholine (ACh)-mediated neurotransmission is fundamental for nervous system function.
- Loss of ACh function, is assoc. with deterioration of cognitive, autonomic & neuromuscular functions
- AChE hydrolyses/inactivates ACh, regulating the concentration of the ACh at the synapse
- Battlefield and environmental exposures can increase AChE transcription thereby decreasing the action of ACh

Exposures

- During the war, soldiers were exposed to harsh climate, anti-AChE insecticides, numerous vaccinations, and battlefield experiences.
- An anti-AChE, pyridostigmine bromide, was given as a prophylactic against chemical warfare
- In short-term peacetime tests, pyridostigmine bromide was deemed safe for the troops, however, it's long-term effects are not known.

Potential Relationships

- Preliminary research suggested a possible role of AChE, Butyrylcholinesterase (BuChE) and Paroxynase (PON), and environmental exposure, as factors in neurological symptoms/muscle weakness
- Animal studies found that stress increases lethality of low levels of an anti-AChE pesticides, suggesting the potential link between stress and AChE activity
- Exposure to anti-AChEs, combined with battlefield experiences, may have contributed potentially to the fatigue, pain, and memory symptoms in GWVI

Biological Mechanisms

- Previous findings are consistent with the idea that stress-induced neuronal signal transduction involves AChE-R overproduction.
- These findings suggest interaction effects with drug responses and exposure to certain chemical compounds that modulate ACh neurotransmission
- Such agents include insecticides (e.g. chlorpyrifos) and therapeutic anticholinesterases).

AChE and Anxiety

- The physiological stress response is expressed primarily in the body's endocrine and neural systems.
- Analysis of AChE activity in Blood samples from 470 individuals (from a normal US population) found a strong correlation with both acute (state) and baseline (trait) anxiety levels.
- As serum AChE levels decreased, the reported levels of anxiety decreased

Objective & Hypotheses

- To determine if mood/anxiety symptoms are related to serum levels of AChE, BuChE, and/or PON among Gulf War deployed and era veterans.
- **Hypotheses:**
  - Serum AChE levels are associated with mood and anxiety symptoms, particularly anxiety.
  - Deployed Gulf War veterans have lower Blood AChE levels than non-deployed.
  - Serum AChE-R ("Readthrough" variant) levels are associated with mood and anxiety symptoms

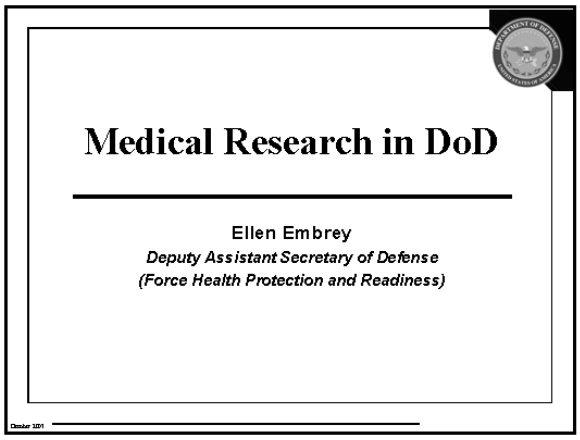
Study Design

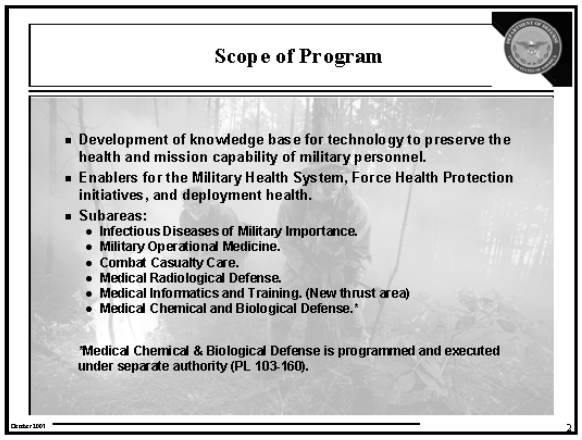
- **Designed to determine any association between blood levels of AChE, BuChE, and PON, and mood/anxiety symptoms in Gulf War era veterans.**
  - Laboratory analysis of stored serum samples will determine levels of AChE, BuChE, and PON among 572 participants in the Iowa Gulf War Cohort Study
  - Laboratory test results will be linked to the health data obtained in the Iowa Gulf War Study and then analyzed to discover any associations that may exist.

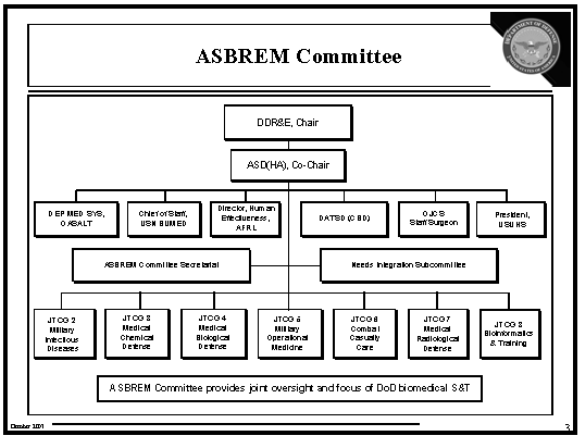
Preliminary Data

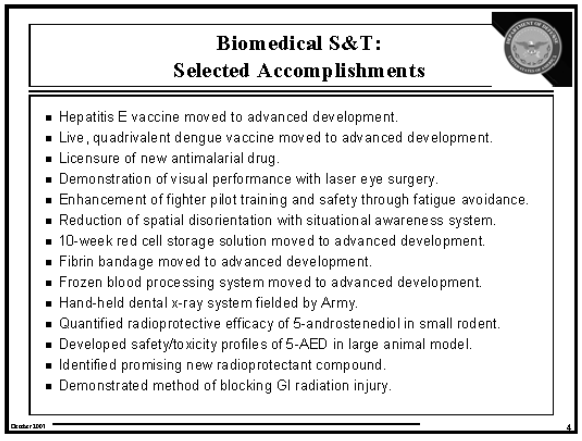
- Initial analyses have been completed on a portion of the Iowa Gulf War Study blood samples.
- Description of Preliminary Data
  - **Dr. Hermona Soreq**

Presentation 9 – Michael Kilpatrick

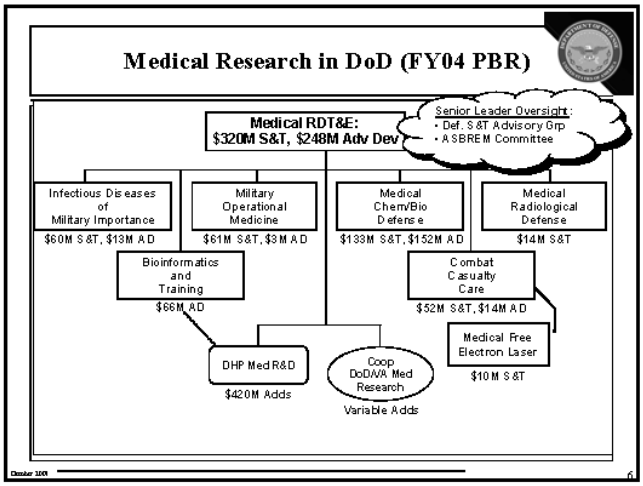


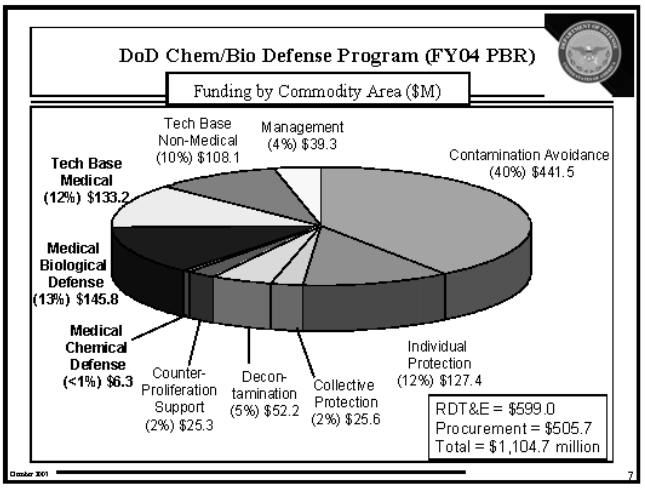


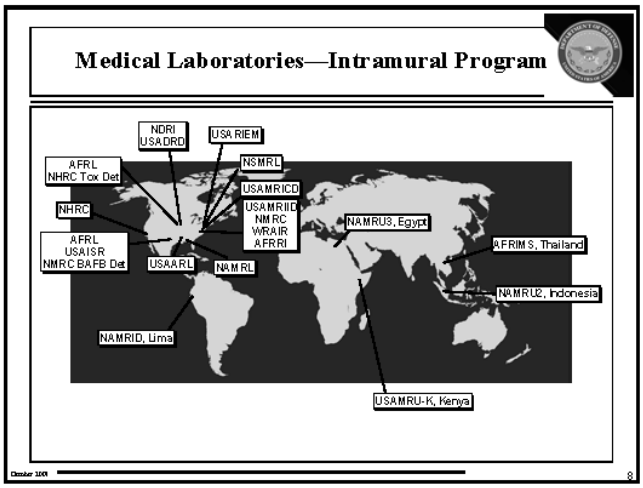





Acquisition/Warfighting Needs
Preparedness for regional conflict.
Preventive medicine.
Life-saving treatment, resuscitative care, and stabilization.
Rapid evacuation to CONUS-based facilities.
Improved logistics and communications.
Enhanced personnel readiness for joint and combined operations.
Theater Medical Health System information technology.
Tactical-to-strategic surveillance.

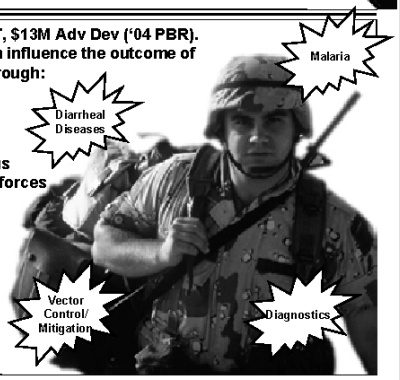

Medical Research in DoD (FY04 PBR)
Medical RDT&E:
$320M S&T, $248M Adv Dev
Senior Leader Oversight:
• Def. S&T Advisory Grp
• ASBREM Committee
Infectious Diseases of Military Importance
$60M S&T, $13M AD
Military Operational Medicine
$61M S&T, $3M AD
Medical Chem/Bio Defense
$133M S&T, $152M AD
Medical Radiological Defense
$14M S&T
Bioinformatics and Training
$66M AD
Combat Casualty Care
$52M S&T, $14M AD
Medical Free Electron Laser
$10M S&T
DHP Med R&D
$420M Adds
Coop DoD/VA Med Research
Variable Adds


DoD Chem/Bio Defense Program (FY04 PBR)
Funding by Commodity Area ($M)
Tech Base Non-Medical (10%) $108.1
Management (4%) $39.3
Contamination Avoidance (40%) $441.5
Tech Base Medical (12%) $133.2
Medical Biological Defense (13%) $145.8
Medical Chemical Defense (<1%) $6.3
Counter-Proliferation Support (2%) $25.3
Decon-tamination (5%) $52.2
Collective Protection (2%) $25.6
Individual Protection (12%) $127.4
RDT&E = $599.0
Procurement = $505.7
Total = $1,104.7 million


Medical Laboratories—Intramural Program
NDRI
USADRD
USARIEM
AFRL
NHRC Tox Det
NSMRL
USAMRICD
NHRC
USAMRIID
NMRC
WRAIR
AFRRI
NAMRU3, Egypt
AFRIMS, Thailand
AFRL
USAISR
NMRC BAFB Det
USAARL
NAMRL
NAMRU2, Indonesia
NAMRID, Lima
USAMRU-K, Kenya

Infectious Diseases of Military Importance

- **Investment: $60M S&T, $13M Adv Dev ('04 PBR).**
- **Infectious disease can influence the outcome of military operations through:**
  - Morbidity
  - Mortality
  - Morale disturbance
  - Use of resources
- **30+ potential infectious disease threats to US forces have been identified.**
- **Primarily addresses diseases that have impacted military operations.**

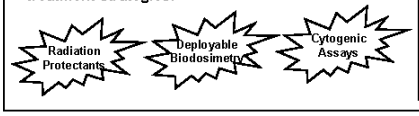


Combat Casualty Care

- **Investment: $52M S&T, $14M Adv Dev ('04 PBR)**
- **Since mid-WWII, 50% of combat deaths have been due to hemorrhage.**
  - Half could have been saved through timely, appropriate care.
  - Ability to rapidly locate, diagnose, treat & monitor during transport is vital.
- **Providing care with a reduced logistics footprint is key.**

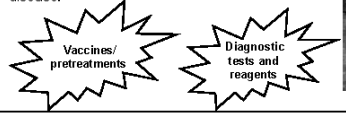
Medical Radiological Defense

- **Investment: $14M S&T ('04 PBR)**
- Need to prevent ionizing radiation injuries in nuclear/radioactive operational environments.
- Need for prophylactic and treatment protocols.
- Need for knowledge of combined NBC risks.
- Need for casualty prediction models.
- Need for biological dosimetry to guide triage and treatment.
- Use of depleted uranium munitions requires assessment of toxicity and development of treatment strategies.



Medical Chemical/Biological Defense

- **Investment: $133M S&T, $152M AD ('04 PBR)**
- **Provide medical solutions for military requirements to protect and sustain the force in a chemical and/or biological warfare environment**
- **Preserve total warfighter effectiveness on a CW/BW battlefield:**
  - Prevent casualties
  - Provide effective treatment of casualties for rapid return to duty
  - Provide rapid, far-forward diagnosis of CW/BW disease.



Bioinformatics and Training

- Investment: $66M AD ('04 PBR)
- Leverages MOM & CCC efforts.
- Surveillance systems to collect and monitor data for disease trends and/or outbreaks.
- Point-of-care PDA for medical reporting and treatment/diagnostic assistance.
- Joint patient DNBI accounting.
- Integration of environmental biosensors, medical surveillance, & communications systems.
- Define, refine & transition technologies & CONOPS that significantly increase responsiveness in consequence management, crisis response, deterrence & intelligence coordination.

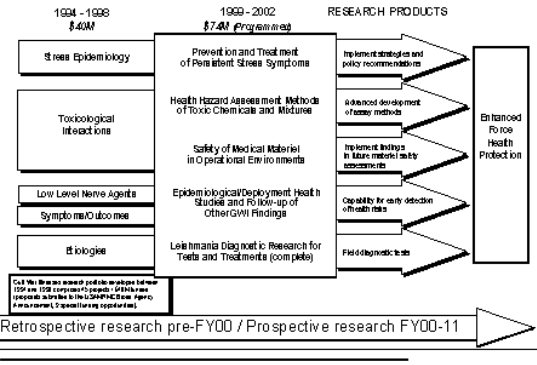
Military Operational Medicine

- Investment: $61M S&T, $3M Adv Dev ('04 PBR)
- Enhance performance for combat success.
- Produce large savings in care and lost duty time.
- Prevent catastrophic injury or failure.
- Save on development of materiel and doctrine.
- Understand consequences of stressors & threats.
- Includes Force Health Protection Research Program (follow-on to GWI Research Program).

Force Health Protection Research Program

- GWIRP was retitled FHPRP in 1999 at request of Assistant Secretary of Defense (Health Affairs) to reflect broader program scope:
  - Shift from retrospective to prospective research.
  - Greater emphasis on prevention.
- Builds on lessons learned from 1991 Gulf War; targets solutions to problems which may arise in future deployments.
- Stimulates forward-looking research to improve force medical protection.
- Links intramural and extramural researchers to bolster intramural science capabilities and to increase extramural institutional interest in military medical research problems.
- Program supported by tri-Service advisory panel; all research receives independent peer review.
- Funding: ~$10M/year.

FHPRP Science Roadmap



FHPRP Mission Focus

OCCUPATIONAL EXPOSURES

- Fuel vapors
- Combustion products (e.g., vehicles)
- Oil well fire smoke
- Altitude
- Sand
- Heat/cold
- Munitions fragments

- Traumatic events
- Anxiety
- Boredom
- Family separation
- Reunion
- Health behaviors

Warfighters are rarely subjected to one stressor at a time yet little research pre-Gulf War had evaluated interactions relevant to military operational environments

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FHPRP Current Investment Focus

- Global Health Monitoring: methods to follow health status from recruitment through deployment and into VA system.
- Health Behavior Interventions: strategies to modify health risk factors (alcohol, tobacco, weight, STDs, unintended pregnancy) that affect military readiness.
- Health Risk Communication: assessment of various methods of providing health risk information.
- Health Risk Assessment: identification of environmental risks important to post-deployment health.
- Medical Materiel Safety: improved safety testing of medical materiel before use in environments where deployment stressors may produce unanticipated effects.

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FHPRP Items of Potential Multi-agency Interest

- Millennium Cohort Study: Long-term, longitudinal collection of data on deployment health from 100,000 service members.
- Studies of neurobehavioral associations and Gulf War symptoms are discovering general mechanisms linking adversity and health outcomes.
- Center for Deployment Health will pioneer methods to monitor post-deployment health of specific military populations.
- Detailed data collection has been initiated for all casualties evacuated out of Afghanistan.
- Follow up will be conducted on patients with embedded depleted uranium.
- The Chem/Bio Defense Program continues to address low-level nerve agent exposure.

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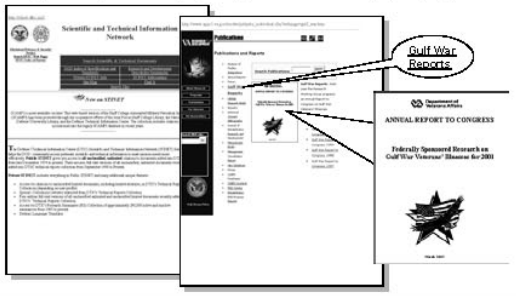
Gulf War Illnesses Research Information Sources

- http://stinet.dtic.mil
- http://appc1.va.gov/resdev/prt/pubs_individual.cfm/webpage=gulf_war.htm



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FHPRP: Selected Accomplishments

- Developed and established DoD Birth Defects Registry for early identification of associations with occupational and deployment exposures.
- Developed diagnostic skin test for Leishmania infection (transitioned to advanced development).
- Discovered apparent absence of blood/brain barrier effect, which is being further evaluated in operational stress conditions.
- Classified some undiagnosed Gulf War veterans' illnesses with symptoms and physiological changes that overlap chronic multi-symptom illnesses (Chronic Fatigue Syndrome and Fibromyalgia).
- Discovered carcinogenic potential of large fragments of imbedded depleted uranium in laboratory animals.
- Discovered new brain stress mechanisms and specific new drug interventions that may be useful in adapting to stress during combat and for modification of adverse health consequences from high-stress conditions.
- Developed test method for squalene antibodies that is being applied to sera of deployed & non-deployed veterans to determine associations with symptoms of illness.
- Discovered potential adverse effects of the administration of multiple vaccines during high stress conditions.

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Military Medical Technology Forecast

- Novel vaccines for debilitating and life-threatening infectious diseases.
- Individual protective equipment based on new understanding of human biomechanics.
- Mobile and flexible life support for long-range evacuation.
- Operational doctrine and ration supplements to improve and sustain operational capability.
- Strategies to protect against ionizing radiation.
- Prediction and prevention of performance degradation and injury.
- Diagnostic and treatment systems for forward medics.
- Novel products for self and buddy control of hemorrhage.
- Advanced treatments for laser eye injury.
- Methods to assess individual psychological stress limits.
- Exposure biomarkers that are sensitive, specific, and easy to use; that can determine personnel exposure; and that can predict health consequences.
- Biologically based health-risk-assessment methods.

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Key to Abbreviations (1 of 2)

- AD: Advanced Development
- CCC: Combat Casualty Care
- CONOPS: Concept of Operations
- CONUS: Continental United States
- Coop DoD/VA Med Res: Cooperative DoD/VA Medical Research Program
- CW/BW: Chemical Warfare/Biological Warfare
- DHP: Defense Health Program
- DNBI: Disease Non-Battle Injury
- GWI: Gulf War Illnesses
- MOM: Military Operational Medicine
- PBR: President's Budget Request
- PDA: Personal Digital Assistant
- RDT&E: Research, Development, Test & Evaluation
- S&T: Science & Technology (basic & applied research)

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Key to Abbreviations (2 of 2): Laboratories

- AFRIMS: Air Force Research Institute of Medicine
- AFRL: Air Force Research Laboratory
- AFRRI: Armed Forces Radiobiology Research Institute
- BAFB Det: Brookes Air Force Base Detachment
- NAMRL: Naval Aerospace Medicine Research Laboratory
- NAMRU: Naval Medical Research Unit
- NDRI: Naval Dental Research Institute
- NHRC Tox Det: Naval Health Research Center, Toxicology Detachment
- NMRC: Naval Medical Research Center
- NSMRL: Navy Submarine Medicine Research Laboratory
- USAARL: US Army Aeromedical Research Laboratory
- USADRD: US Army Dental Research Detachment
- USAISR: US Army Institute of Surgical Research
- USAMRICD: US Army Medical Research Institute of Chemical Defense
- USAMRIID: US Army Medical Research Institute of Infectious Diseases
- USAMRU: US Army Medical Research Unit
- USARIEM: US Army Research Institute of Environmental Medicine
- WRAIR: Walter Reed Army Institute of Research

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Presentation 10 – Robert Sheridan

Health Effects of Low-dose Chemical Agent Exposure

28 October 2003

Presenter: Robert E. Sheridan

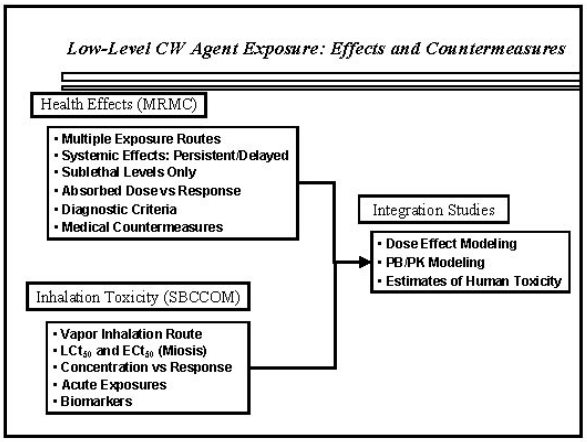
USAMRICD

Low-Level CW Agent Exposure: Effects and Countermeasures

Health Effects Study Goals:

- Generate a SCIENCE BASE to understand the underlying effects of low-level exposure to CW agents (TC1).
- Develop METRICS to identify pathophysiology due to low-level exposure to CW agents (TC2).
- Develop/evaluate prophylactics and therapeutics, as required (TC3).

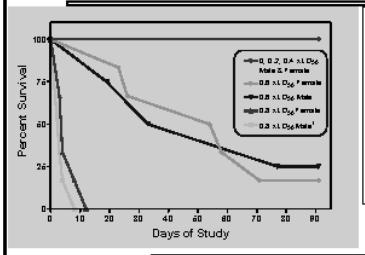
Low-Level CW Agent Exposure: Effects and Countermeasures



Low-Level CW Agent Exposure: Effects and Countermeasures

- **Pathology (LOAEL/NOAEL): *Primary Concern***
  - Cognitive/behavioral changes
  - Tissue lesions/degeneration
  - Cardiac arrhythmias/nerve function
- **Biomarkers (LOEL/NOEL): *Secondary Concern***
  - Inhibition of blood, muscle, and brain cholinesterases
  - Inhibition or induction of "other" proteins
  - Changes in mRNA expression patterns
- **Transient vs. Persistent vs. Delayed Effects**

Low-Level CW Agent Exposure: Effects and Countermeasures



Maximum Tolerated Doses of GB, GD, GF, VX (shown), and VR.

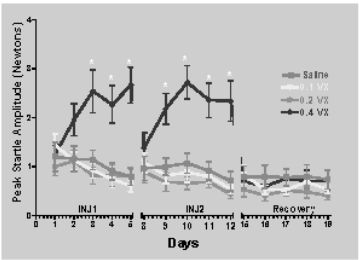
Exposure below this dose:

- **No clinical signs of toxicity**
- **No delayed peripheral neuropathy**
- **No changes in complete blood cell counts**
- **No changes in blood chemistries other than AChE inhibition**
- **No histopathology developed in liver, brain, heart, lung, kidney, muscle, nerve.**

AGENT	ACUTE LD50 (µg/kg)	Daily MTD (µg/kg)
GB	42	16
GD	28	11
GF	55	22
VX	9	2
VR	11	4

Low-Level CW Agent Exposure: Effects and Countermeasures

Changes in Acoustic Startle Responses in guinea pig:



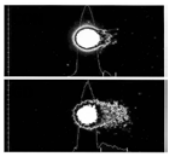
Acoustic Startle Response in guinea pig:

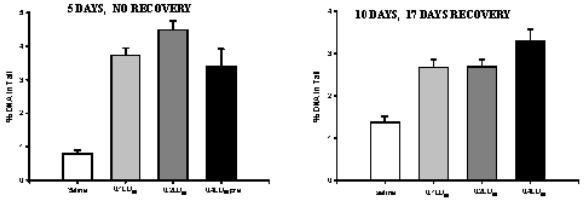
- **Effects @ ≥ MTD**
- **No effect @ < MTD**
- **Effect increases with repeated daily exposures for GD and VX**
- **Rank order of effect VX>GD>GB**
- **Reverses within 72 hours**

Low-Level CW Agent Exposure: Effects and Countermeasures

Some low-level CW agent effects are not currently associated with obvious pathology:

- **Apoptosis in peripheral leukocytes from exposed guinea pigs**
- **No changes in CBC detected**
- **Implications for immunosuppression being investigated.**





		≥MTD	<MTD
Neurological	FOB/Gait Anomalies:		
	GB	+	-
	EEG (delta/sleep):		
	GB	+	-
Behavioral	Acoustic Startle:		
	GB	+	-
	GD	++	-
	VX	+++	-
	Active Avoidance:		
	GB	-	-
	GD	+	-
	Progressive Ratio:		
	GB	-	-
	GD	-	-
	Spatial Memory:		
	GB	+	-
Molecular	Leukocyte Apoptosis:		
	GD	++	++

Low-Level CW Agent Exposure: Effects and Countermeasures

Current Status:

- Repetitive doses of CW Agents appear to be the more likely to cause adverse health effects than single doses.
- Most significant adverse health effects have been developed at clinically symptomatic exposures to CW Agents.
- Some biochemical and genomic changes have been noted at doses less than the MTD.

Low-Level CW Agent Exposure: Effects and Countermeasures

Future Priorities:

- Confirm pathological/non-pathological exposure levels for single CW Agents.
- Evaluate efficacy of existing/planned therapeutics on LOAEL (pathological) effects.
- Evaluate persistence of LOEL (non-pathological) changes for use as possible diagnostic markers of exposure.

Presentation 11 – Eugene Oddone

Occurrence of Amyotrophic Lateral Sclerosis (ALS) Among Gulf War Veterans (CSP#500)

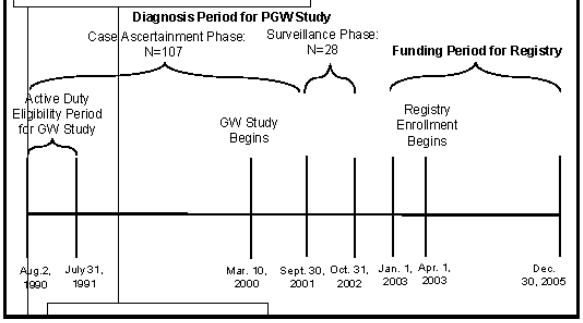
National Registry of Veterans with ALS (CSP#500A)

Funded by the Department of Defense, and
Office of Research and Development,
Cooperative Studies Program,
Department of Veterans Affairs

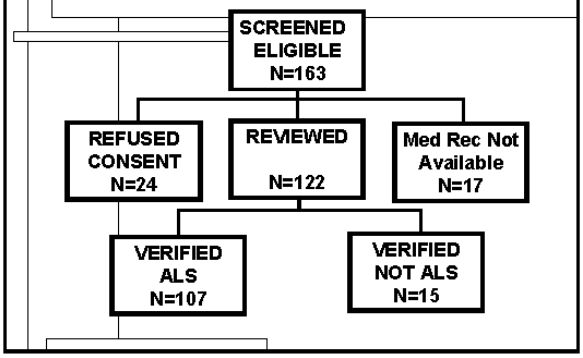
Eugene Oddone, MD, MHSc; R. Horner (original PI)

ERIC
EPIDEMIOLOGIC RESEARCH & INFORMATION CENTER
DURHAM, NC

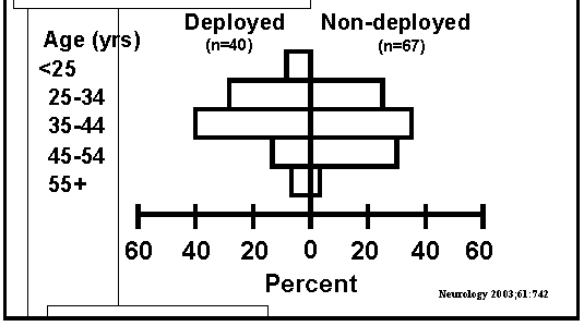
Timeline of Veterans ALS Studies: Durham ERIC



ALS in GW Vets: Case Finding



Age at Onset: ALS Cases by Deployment Status

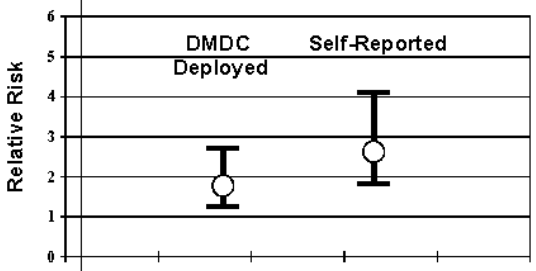


Age-Specific Rates (per 100,000) of ALS by Deployment Status

Age at Onset	Men, W. WA State	Non-deployed (n=67)	Deployed (n=40)
<25	0.11	0.00	0.08
25-34	0.79	0.26	0.45
35-44	1.63	0.80	1.77
45-54	2.49	4.81	5.64
55-64	6.42	8.89	31.19

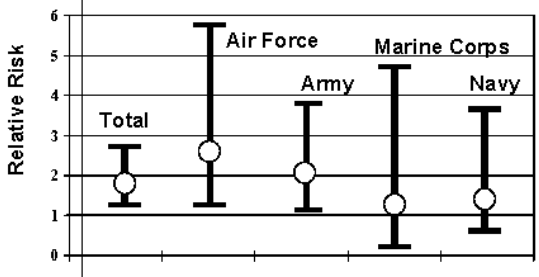
Neurology 2003;61:742

ALS in GW Vets: Adjusted Relative Risk of ALS



Neurology 2003;61:742

ALS in GW Vets: Branch-Specific Adjusted Relative Risks of ALS DMDC Deployment



Neurology 2003;61:742

ALS in GW Vets: Surveillance Update

- 28 verified ALS cases
  - DMDC Status: 10 Deployed, 18 Non-deployed
  - Self-Report Status: 14 Deployed, 14 Non-deployed
  - Reanalysis did not alter original RR
  - Ongoing analyses of age-adjusted and branch-specific rates

ALS in GW Vets: Estimates of Under-Ascertainment of ALS Cases

- Capture-recapture methodology applied to estimate under-ascertainment among deployed and non-deployed personnel
- ⇨ Evidence for differential undercount
  - modest under-ascertainment among non-deployed
  - little under-ascertainment among deployed
- ⇨ Age-adjusted risk of ALS among deployed remains elevated after correcting rates for under-ascertainment

ALS in GW Vets: Summary of Exposure and Biological Data

- DNA: Analyzed at Lexington, KY VAMC, Edward Kasarskis, MD. Ph.D.
- In-home interview of exposures (occupational, health, chemical, food): Oregon Health & Science University, Peter Spencer, Ph.D.
- Oil well fire exposure: Army Center for Health Promotion and Preventive Medicine, Jack Heller, Ph.D.
- Blood and urine heavy metals: Centers for Disease Control & Prevention, Drue Barrett, Ph.D.

ALS in GW Vets : Planned Manuscripts

- Clinical description of cases
- Capture/recapture (under-ascertainment of cases)
- Oil well fire exposure and GIS analysis among deployed veterans
- Incubation period/epidemic curve
- Methodological challenges of investigating a rare disease
- Blood and urine heavy metal analyses

National Registry of Veterans with ALS (CSP #500A)

Funded by the Office of Research and Development, Cooperative Studies Program, Department of Veterans Affairs

Eugene Z. Oddone, M.D., M.HSc.
Edward J. Kasarskis, M.D., Ph.D.

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VA Medical Center
LEXINGTON, KY

ALS Registry Objectives

- **Identify all living veterans with a diagnosis of ALS and track their health status**
- **Include veterans in ALS-related research**
  - Clinical drug (or other interventional) trials
  - Epidemiological studies
  - Genetic studies **(DNA component pending approval)**

Scientific Review Committee: Veterans ALS Registry

John Booss, MD National Director of Neurology Department of Veterans Affairs	Kimberly A. Gray, PhD Health Scientist Administrator NIEHS
Robert H. Brown, Jr., MD, D.Phil Director, Day Neuromuscular Research Laboratory Massachusetts General Hospital	Philip W. Lavori, PhD Acting Director, Cooperative Studies Program Director, DNA Coordinating Center Department of Veteran Affairs
Lucie Bruijn, PhD Science Director and Vice President ALS Association	Hiroshi Mitsumoto, MD Director, Eleanor and Lou Gehrig MDA/ALS Center Columbia-Presbyterian Medical Center
Louis D. Fiore, MD, MPH Co-Director, Massachusetts Veterans Epidemiologic Research and Information Center Department of Veterans Affairs	Lorene Nelson, PhD Associate Professor of Health Research and Policy Stanford University
Ronnie D. Horner PhD Program Director Health Disparities Research NINDS	Margaret Pericak-Vance, PhD Director, Center for Human Genetics Duke University Medical Center

Identification of Cases Veterans ALS Registry

- **Previously identified Gulf War veterans**
- **Extant VA databases: Inpatient Treatment File (PTF), Outpatient Clinic File (OPC)**
  - Based on ICD-9 code for ALS (335.20)
- **Referrals from Veterans Benefits Administration**
- **Ongoing nation-wide solicitation of cases**
  - ALS Association, VA Neurology Service, Veterans Service Organizations, American Academy of Neurology

Screening and Case Verification Veterans ALS Registry

- **Initial telephone screening to ascertain veteran status and self-report of ALS diagnosis (Durham ERIC)**
- **Consent, medical record release, and physician contact forms mailed following telephone screening**
- **Medical records obtained and reviewed by expert neurologists (Lexington and Durham)**

Baseline and Follow-Up Interviews
Veterans ALS Registry

- **Baseline Interview: following medical record verification of ALS**
  - ALS Functional Rating Scale
  - Military and Occupational History
  - Medication List
- **Follow-up interviews: every six months**
  - ALS Functional Rating Scale
  - Medication List
  - Use of feeding tube and ventilation assistance

Current Status
Veterans ALS Registry

- 658 Screened by Phone/Web: 552 Eligible
- 80 of 552 (15%) Verified ALS: Enrolled
- 472 in process of verification
- Additional 770 individuals have been identified in VA databases, screening is ongoing

Gulf War Veteran Participants
Veterans ALS Registry

- **58 veterans from Gulf War ALS study currently enrolled in Registry**
  - 90% of living/found veterans from original
- **Additional 21 veterans have screened eligible for the Registry and also reported being deployed to the Gulf during the Gulf War period**
  - Note: These cases not yet verified by medical record review, and deployment status has not been confirmed by military records (self-report only)

Data Access Procedures
Veterans ALS Registry

- **VA and non-VA investigators may request access to data from Registry via a brief Statement of Research Intent**
- **If approved by the Registry, investigators will submit a complete proposal**
- **The Scientific Review Committee will review all proposals and make recommendations for acceptance**

DNA Banking Veterans ALS Registry

- Gene and gene x environment interactions may be one of the most promising areas for research on etiology of ALS
- Registry Scientific Review Committee supported addition of DNA banking
- Proposal for DNA banking has been submitted to VA Cooperative Studies Program DNA Coordinating Committee and is currently under review

Proposed Projects Using Registry Data

- Addition of control subjects to Registry, including control DNA
  - NIEHS Grant Submission
- Case control study of gene and gene x environment interactions in ALS
  - NINDS and NIEHS Grant Submission
- Identification of biomarkers of ALS onset and progression
  - NINDS Grant Submission
- Identification of metabolic signatures in ALS
  - NINDS Grant Submission

Presentation 12 – Susan Perez

Veterans Benefits Administration
Data and Information Services

GULF WAR VETERANS
INFORMATION SYSTEM (GWVIS)

GWVIS

Briefing For:

Department of Veterans Affairs
Research Advisory Committee
On Gulf War Veterans' Illnesses

October 28, 2003

Prepared by VBA/DSIS October 2003 2

Briefing Overview

Four Main Topics Requested by the RAC:

- VBA
- PA&I
- GWVIS
- Gulf War data

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VBA Overview

- VBA adjudicates claims
- VBA claims process
- VBA does not diagnose veterans
- VBA maintains data about decisions

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PA&I Overview

Office of Performance Analysis and Integrity (PA&I):

- List of 5.8 million Gulf War service members, from 1990 to present
- Data on how many veterans have a claim with a decision
- VBA diagnostic code data for those claims with a decision

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PA&I Overview

Data limitations:

- Current VBA awards system limitation- does not hold all diagnostic codes
- Diagnostic code ≠ ICDM-9 code
- PA&I counts number of veteran deaths, but does not conduct mortality studies
- This is raw data not subjected to analysis

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Purpose of GWVIS

- Identifies Gulf War service member population and key sub-populations
- Monitors Gulf War veteran compensation and pension benefit use
- Provides data for quarterly reports
- Serves as a resource for *ad-hoc* data requests about Gulf War veterans

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GWVIS Data Sources

Defense Manpower Data Center (DMDC)

- Identifies Active Duty and Ready Reserve service members since August 2, 1990
- Identifies Gulf War deployment status

Veterans Benefits Administration (VBA)

- Identifies granted, denied, and pending compensation and pension claims
- Identifies deaths

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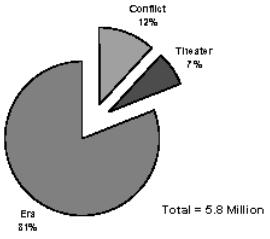
Gulf War Service Members



With a least one day Active or Reserve Duty from 8/2/90 to the present

Source: GWVIS August 2003

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Gulf War Veteran Data

Specific data requested by the RAC:

- **Gulf War veterans with at least one day of active duty from 8/2/90 - 7/31/91 and a processed claim for any VBA benefit**
- **Gulf War veteran claim demographic data**
- **Gulf War veteran claim data for three VBA diagnostic codes**

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Specific RAC Data Request

Three New Deployment Categories:

- **First Deployment to SWA Between 8/2/90 - 7/31/91**
- **First Deployment to SWA Between 8/1/91 - 10/1/02 and one day of Active Duty 8/2/90 - 7/31/91**
- **No Deployment to SWA and one day of Active Duty 8/2/90 - 7/31/91**

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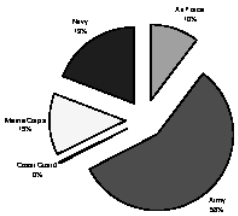
Demographics of Claims Processed by Branch of Service

First Deployment to SWA Between 8/2/90 - 7/31/91



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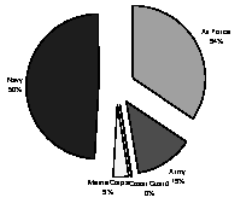
Demographics of Claims Processed by Branch of Service

**First Deployment to SWA Between 8/1/91 - 10/1/02
And one day of Active Duty 8/2/90 - 7/31/91**



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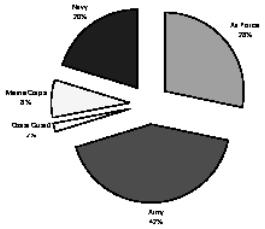
Demographics of Claims Processed by Branch of Service

**No Deployment to SWA
And one day of Active Duty 8/2/90 - 7/31/91**



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Demographics of Claims Processed by Sex and Age

**Veterans with one day of Active Duty 8/2/90 – 7/31/91
and a processed claim**

Category		First Deployment to SWA Between 8/2/90 - 7/31/91		First Deployment to SWA Between 8/1/91 - 10/1/02		No Deployment to SWA	
		Count	Percent	Count	Percent	Count	Percent
Claims Processed		245,546	100	77,669	100	519,023	100
Sex	Female	21,161	8.6	6,894	8.9	81,992	15.8
	Male	223,726	91.1	70,272	90.5	435,739	84.0
	Unknown	658	0.3	503	0.6	1,292	0.2
Age	< 44	162,808	66.3	50,360	64.8	282,674	54.5
	≥ 45	82,427	33.6	27,292	35.1	236,214	45.5
	Unknown	310	0.1	17	0.0	135	0.0

Prepared by VBA/DQIS October 2003 — 15

Demographics of Claims Processed by Race/Ethnicity

**Veterans with one day of Active Duty 8/2/90 – 7/31/91
and a processed claim**

Category		First Deployment to SWA Between 8/2/90 - 7/31/91		First Deployment to SWA Between 8/1/91 - 10/1/02		No Deployment to SWA	
		Count	Percent	Count	Percent	Count	Percent
Claims Processed		245,546	100	77,669	100	519,023	100
Race / Ethnicity	American Indian or	1,593	0.6	530	0.7	9,696	1.9
	Asian or Pacific Islander	6,325	2.6	3,310	4.3	6,646	1.3
	Black, not Hispanic	65,325	26.6	14,768	19.0	112,597	21.7
	White, not Hispanic	154,130	62.8	53,588	69.0	347,545	67.0
	Hispanic	13,514	5.5	4,131	5.3	24,430	4.7
	Other	3,868	1.6	807	1.0	7,539	1.5
	Unknown	790	0.3	535	0.7	2,581	0.5
	Blank	0	0.0	0	0.0	7,989	1.5

Prepared by VBA/DQIS October 2003 — 16

Gulf War Veteran Data

Claim data for three VBA diagnostic codes:

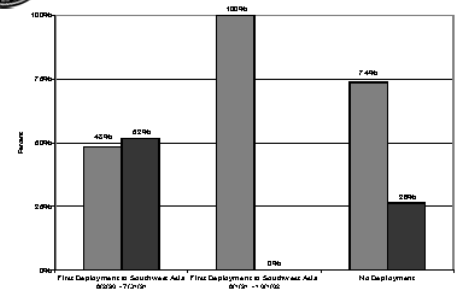
- **Gulf War veteran service-connection and nonservice-connection percentages for ALS, MS, and Tinnitus claims**
- **Gulf War veterans with at least one day of active duty from 8/2/90 - 7/31/91 and a processed claim for any VBA benefit**

Gulf War Veteran Data

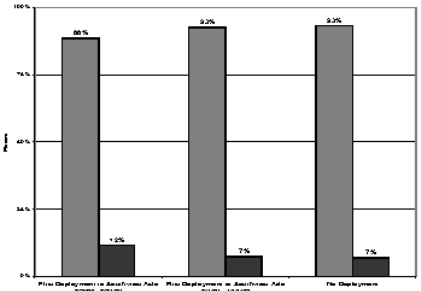
Veterans with one day of Active Duty 8/2/90 – 7/31/91 and a processed claim

Category		First Deployment to Southwest Asia 8/2/90 - 7/31/91		First Deployment to Southwest Asia 8/1/91 - 10/1/02		No Deployment	
		Count	Percent	Count	Percent	Count	Percent
Claims Processed		245,845	100	77,669	100	519,023	100
ALS DC 8017	Service-Connected	28	0.48	7	1.00	42	0.74
	Nonservice-Connected	30	0.52	0	0.00	15	0.26
	Total Claims	58	100	7	100	57	100
MS DC 8018	Service-Connected	360	0.88	126	0.93	1,155	0.93
	Nonservice-Connected	47	0.12	10	0.07	87	0.07
	Total Claims	407	100	136	100	1,242	100
Tinnitus DC 6260	Service-Connected	22,013	0.81	10,443	0.88	49,051	0.86
	Nonservice-Connected	5,131	0.19	1,436	0.12	8,931	0.15
	Total Claims	27,144	100	11,879	100	57,982	100

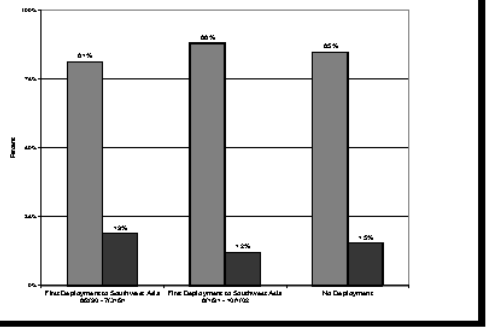
Amyotrophic Lateral Sclerosis (ALS) Grant and Denial Rates



Multiple Sclerosis (MS) Grant and Denial Rates



Tinnitus
Grant and Denial Rates



Questions?

Please contact:

Susan Perez, Assistant Director,
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(202) 273-6811
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http://vbaw.vba.va.gov/bl/20/opai/

Presentation 13 – Denise Hynes

Overview of VHA Information Systems Available for Research

Presentation to the Research Advisory Committee for Gulf War Veterans' Illnesses

October 28, 2003

Denise Hynes, PhD, RN
Director, VA Information Resource Center

1

VHA Information Systems

- Local Facility Level: Information May Only Reside At Local Facility
- Corporate (National) Level: Some Local Data Are Mandated And May Include Uploading To A Central Location
- VA Network Level: VISN Warehouses
  - Above local level, below corporate level

2

Multiple Health Data Sources

- Administrative data
- Medical record information
- Patient-derived data
- Provider and facility data
- Pharmaceutical data

3

Uses of VA Data

- Patient, employee and provider satisfaction
- Quality of care
- Access to care
- Resource use
- Operational efficiency
- Cost of care

4

Examples of Health Measures

- Post-discharge mortality
- Functional status
- Rates of complication and/or readmission
- Length of stay, length of recovery
- Cost effectiveness

5

Highlights of VA Data

- Centralized resources for many databases
- Readily available for VA researchers
- Available for large groups of patients
- Given good coding, reflective of general clinical status
- Common identifiers allows linking across care continuum and over time

6

Caveats About VA Data

- Limitations of ICD-9-CM coding
- Incomplete picture of all care dimensions
- Incentives to coding
- Retrospective nature of discharge abstracts and diagnoses
- Limited access to data
- No public use files

7

Sources of Data Available for Research

- Administrative data
- Hospital/facility-level data
- Medical record information
- Patient-derived data

8

Comprehensive Listing of VA Databases

Corporate Database Monograph

- Produced by VHA OI Information Assurance National Data Systems
- Last updated in 2003
- http://vaww.ia.med.va.gov/nds/Corporate_Database_Inventory.htm

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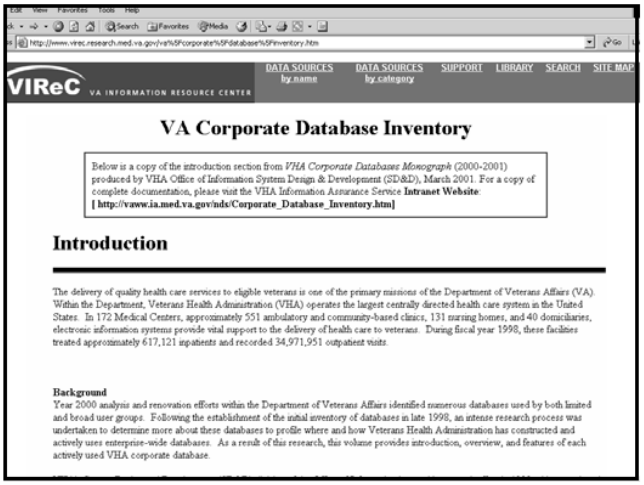

VA Databases Often Used in HSR

- National Patient Care Data (NPCD) Files
  - Outpatient Medical SAS Files
  - Inpatient Medical SAS Files or Patient Treatment Files (PTF)
- Veterans Health Information System Architecture (VistA)
  - Patient Level Clinical Data

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VA Databases Often Used in HSR

- Prescription Use – Pharmacy Benefits Management Data
- Decision Support System (dSs) Data
- Beneficiary Identification Record Locator System (BIRLS)
- Survey Data Files
  - National Survey of Veterans
  - Census 2000

12

New Databases

- DSS Clinical data Extracts
  - Fact of Lab
  - Lab results
  - Prescription Fills
  - Fact of Radiology
- HERC Average cost datasets
- VA-Medicare Linked Data

13

Highlights of Selected Databases

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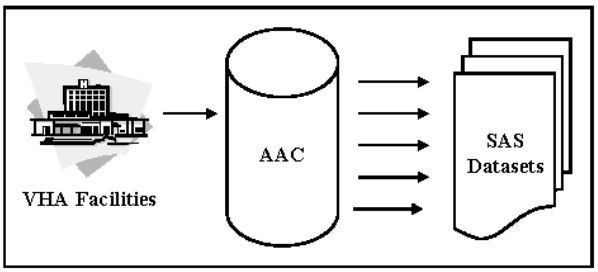
NPCD Overview

- Local facilities transmit data to the Austin Automation Center
- Data stored in relational database, Oracle
- Generates SAS system files for inpatient and outpatient data and other "specialty" areas

15

Local to National Data Flow



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Data Elements In All Inpatient Datasets

- Patient identifier (SCRSSN)
- Facility & VISN identifiers of where care provided
- Admission & Discharge Date & Time
- Discharge Type (e.g., Regular, Death-Autopsy, Non-bed Care)
- Primary Diagnosis for stay (DXLSF)

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Data Elements Common In Outpatient Datasets

- Patient identifier (SCRSSN)
- Patient demographics (Age, date of birth, race, marital status)
- Patient Zip Code, County, & State of Residence
- Date of encounter

18

Common Data Elements

- Means Test Indicator
- Patient eligibility code (Separate vet and non-vet categories)
- Agent Orange exposure claimed
- Radiation exposure claimed

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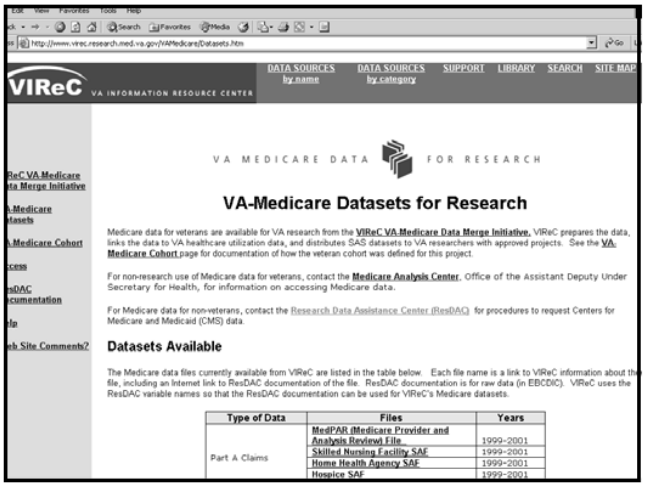

VHA Clinical Data: Local and Corporate Level

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Locally Available Clinical Data

Clinical management info entered in the local point of care information system

- Examples at point of care:
  - Computerized Patient Record System (CPRS)
  - VistA (Formerly DHCP)
  - Clinical Reminders

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VistA Limitations

- Includes only services provided at that facility
- For a multi-site study, requires extracting data from multiple local sites
- Difficult to link patient data across VistA software packages covering different units, e.g., pharmacy, lab, radiology

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VistA Limitations

- Some clinical software outside of VistA system (eg. Some cardiac cath lab)
- Some software may be implemented differently at sites
- Text–based data not easily extracted
  - (e.g., EKG, radiology interpretation, H&P)
- Some clinical data are not entered
  - (e.g., smoking hx, alcohol use)

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VistA 5-Year Plan

- Increased use of standard coding systems
- Plans for new data entry (e.g., images, results from clinical procedures such as ECG, etc.)
- Improved numeric identifier that serves as an enterprise-wide identifier for patients and providers
- Plans for a Health Data Repository will support extracting of data for both corporate reporting and research (2005)

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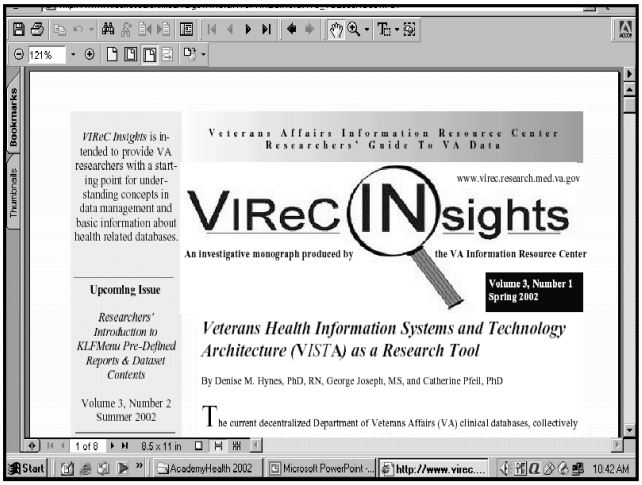

VIReC Insights is intended to provide VA researchers with a starting point for understanding concepts in data management and basic information about health related databases.

Upcoming Issue

Researchers' Introduction to KLFMenu Pre-Defined Reports & Dataset Contents

Volume 3, Number 2
Summer 2002

Veterans Affairs Information Resource Center
Researchers' Guide To VA Data

www.virec.research.med.va.gov

VIReC INsights

An investigative monograph produced by the VA Information Resource Center

Volume 3, Number 1
Spring 2002

Veterans Health Information Systems and Technology Architecture (VISTA) as a Research Tool

By Denise M. Hynes, PhD, RN, George Joseph, MS, and Catherine Pfeil, PhD

The current decentralized Department of Veterans Affairs (VA) clinical databases, collectively

Corporate-Level Registries: Examples

- Immunology Case Registry
  - AIDS Service
- Ionizing Radiation Registry
  - Env Agents Svc
- VA National Clozapine Registry
  - Mental Health & Behav Sciences Svc
- VA Central Cancer Registry
  - Acute Care, Med Svc

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Other Corporate Examples

- Functional Status and Outcome Database
  - PM&R Svc
- Emerging Pathogens Initiative
  - Acute Care, Med Svc
- Home Based Primary Care
  - G&EC
- External Peer Review Program Data
  - OQP

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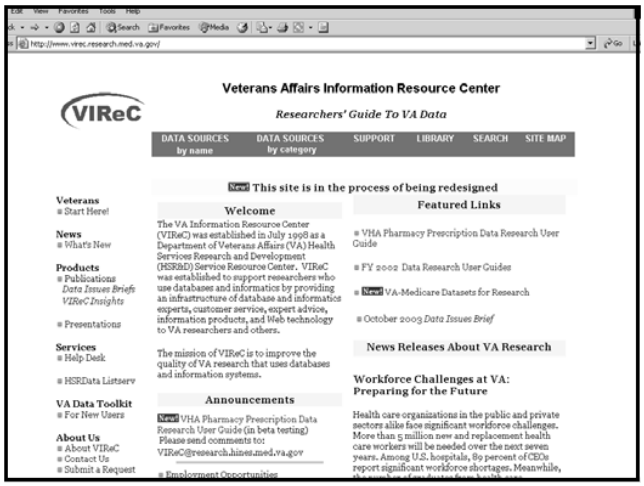

VIReC Mission/Purpose

- To Promote an Environment of Information Sharing About Using Data
- To Serve the Research Community With Their Health Data Information Needs

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About VIReC

- Provides research assistance to VA data users
- Established in 1998
- Funded by VA HSR&D Service
- Located at Hines VA Hospital

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Presentation 14 – Clare Mahan

ANTHRAX VACCINATION AND SELF-REPORTED SYMPTOMS, FUNCTIONAL STATUS AND MEDICAL CONDITIONS IN THE NATIONAL HEALTH SURVEY OF GULF WAR ERA VETERANS AND THEIR FAMILIES

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Han K. Kang, Dr. P.H.
Nancy A. Dalager, M.S.
Jack M. Heller, Ph.D.

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US Army Center for Health Promotion and Preventive Medicine (CHPPM), Aberdeen Proving Ground, MD

NATIONAL HEALTH SURVEY POPULATION

- Phase I – questionnaire mailed to 30,000 veterans
  - 15,000 Gulf
  - 15,000 Non-Gulf
- 15,817 respondents from Phase I
- Phase II – telephone interviews of non-respondents
- 5,100 respondents from Phase II
- 70% over all response rate (N=20,917)
  - 11,441 Gulf
  - 9,476 Non-Gulf

QUESTIONNAIRE FOR NATIONAL HEALTH SURVEY OF GULF WAR-ERA VETERANS AND THEIR FAMILIES

- Functional impairment
- Limitation of employment
- Clinic visit during past year
- Hospitalization during past year
- Self-report symptoms inventory of 48 items
- Symptoms coded as none, mild, or severe
- Self-report of 31 medical conditions present during past 12 months

COMPARISION GROUPS

N= 4601 self-report, received anthrax vaccination	(40.2%)
N= 3861 self-report, unknown if received anthrax vaccination	(33.7%)
N= 2979 self-report, did not receive anthrax vaccination	(26.0%)
N= 352 anthrax vaccination record on file with DoD	
N= 11,441 all Gulf veterans	

OBJECTIVE

COMPARE:

- Functional status
- Medical care utilization
- Symptoms
- Chronic disease status

of Gulf War veterans for whom anthrax vaccination records exist to Gulf veterans who self-reported "no" s/he had not received anthrax vaccination.

TABLE 1. Percent distribution of selected characteristics for 11441 Gulf War veterans according to self-report of anthrax vaccination and for exposed group documented to have received anthrax vaccination

Characteristics	Anthrax Vaccination			
	S-R Yes (N=4601)	S-R Unknown (N=3861)	S-R No (N=2979)	Documented DoD (N=352)
Gender				
Male	78.6	83.6	82.8	71.6
Female	21.4	16.4	17.2	28.4
Age (mean age in yrs in 1991)	30.8	29.8	30.7	31.5
(interquartile range)	23-37	23-35	24-36	23-39
Race				
White	74.9	71.5	74.7	77.0
Black	18.2	20.3	18.6	15.3
Other	6.8	8.2	6.7	7.7
Marital status				
Single	41.5	44.3	40.6	49.7
Married	52.4	50.8	54.9	44.3
Other	6.1	4.9	4.5	6.0
Rank				
Officer	13.2	8.3	16.4	13.6
Warrant	1.6	1.3	0.8	2.0
Enlisted	85.2	90.4	82.8	84.4

TABLE 1. Percent distribution of selected characteristics for 11441 Gulf War veterans according to self-report of anthrax vaccination and for exposed group documented to have received anthrax vaccination (cont'd)

Characteristics	Anthrax Vaccination			
	S-R Yes (N=4601)	S-R Unknown (N=3861)	S-R No (N=2979)	Documented DoD (N=352)
Branch of Service				
Air Force	8.6	9.4	22.4	3.4
Army	74.4	64.6	44.3	96.6
Marine	11.3	12.6	9.1	0.0
Navy	5.7	13.4	24.2	0.0
Unit Type				
Active Duty	28.6	38.5	49.1	4.8
National Guard	31.2	28.8	23.3	22.4
Reserve	40.2	32.7	27.6	72.7
Alcohol use (past 12 months)	76.1	75.6	76.6	75.6
Cigarettes (past 12 months)	34.9	35.7	32.3	31.2
Number of Vaccines (other than anthrax)				
0	10.5	37.1	29.3	19.6
1	20.8	27.4	27.3	22.4
2	26.8	20.6	25.8	23.0
3	21.5	11.0	13.3	20.7
4	10.5	3.4	3.6	11.1
5	7.9	0.4	0.7	3.1

TABLE 2. Prevalence and adjusted odds ratios of functional impairment, limitation of employment, and medical care utilization due to illness among 11,441 Gulf War veterans according to self-report of anthrax vaccination, plus 352 Gulf War veterans for whom anthrax vaccination is documented in DoD

	Self-Reported Anthrax Vaccination			Documented	Adjusted Odds Ratio (95%CI)		
Conditions	Yes (N=4601)	Unknown (N=3861)	No (N=2979)	DoD (N=352)	Anthrax Vaccination Yes[†]	Unknown[†]	DoD[‡]
Functional Impairment	32.7	28.6	19.1	26.0	1.73 (1.54-1.96)	1.53 (1.41-1.79)	1.20 (0.91-1.60)
Limitation of Employment[§]	21.3	17.9	10.2	17.3	2.13 (1.83-2.48)	1.86 (1.60-2.16)	1.56 (1.12-2.17)
Clinic Visits	55.7	48.4	45.6	54.3	1.36 (1.22-1.50)	1.14 (1.04-1.26)	1.25 (0.97-1.60)
Hospitalization[¶]	8.8	7.6	6.3	9.4	1.22 (1.00-1.48)	1.21 (0.99-1.47)	1.34 (0.89-2.01)

† Positive response to the question, "Thinking back over the past 2 weeks, did you stay in bed or at home all or part of any day because you did not feel well or as a result of illnesses or injury?"

‡ Positive response to the question, "Are you limited in your employment or the kind of work you can do or around the house because of any impairment or health problems?"

§ Clinic visit because of illness during past 12 months.

¶ Hospitalization because of illness during past 12 months.

¦ CI: Confidence Interval

†Adjusted odds ratios (95% CI) were derived from logistic models. Reference category was self-report "No." Adjustment was made for number of vaccines received other than anthrax (0,1, ..5); gender (male vs. female); age in 1991 (<30 vs. ≥ 30 yrs.); race (white vs. other); marital status (single vs. ever married); rank (officer or warrant vs. enlisted); branch of service (non-ground troops vs. ground troops); unit component (active duty vs. National Guard or Reserves); current alcohol use (within past 12 months); and current cigarette use (within past 12 months).

‡Adjusted odds ratios (95% CI) for documented vaccination by DoD records relative to self-report "No" were derived through stratified Cochran-Mantel-Haenszel (1 5) analysis. Adjustment was made for variables that were correlated with both exposure (anthrax vaccine) and outcome (condition). These confounding factors included number of vaccines received other than anthrax, (≤ 2 vs. ≥ 3); gender (male vs. female); branch of service (non-ground troops vs. ground troops); unit component (active duty vs. National Guard or Reserves).

TABLE 3. Prevalence and adjusted odds ratios of selected self-reported medical conditions among 11,441 Gulf War veterans according to self-report of anthrax vaccination, also for 352 Gulf War veterans for whom anthrax vaccination is documented in DoD records.

Conditions	Self-Reported Anthrax Vaccination: Yes (N=4601)	Unknown (N=3361)	No (N=2975)	Documented DoD (N=352)	Adjusted Odds Ratio (95% CI) †: Anthrax Vaccination Yes†	Unknown†	DoD*
Dermatitis	34.9	28.4	18.7	29.7	1.85 (1.64-2.09)	1.62 (1.44-1.83)	1.35(1.06-1.72)
Gastritis	30.8	27.4	18.1	28.5	1.85 (1.64-2.09)	1.55 (1.38-1.75)	1.48(1.11-1.92)
Arthritis	29.9	24.2	18.6	26.4	1.51 (1.33-1.70)	1.30 (1.14-1.47)	1.22(0.93-1.62)
Frequent diarrhea	29.5	23.5	13.8	23.8	1.93 (1.69-2.20)	1.69 (1.48-1.93)	1.35(1.03-1.86)
Hair loss	22.0	19.8	11.8	16.3	1.87 (1.62-2.16)	1.73 (1.50-1.99)	1.25(0.90-1.73)
Migraines	21.2	19.1	13.6	16.9	1.42 (1.23-1.63)	1.31 (1.19-1.57)	0.96(0.69-1.34)
Lumbago	18.5	16.3	9.4	14.4	1.83 (1.55-2.14)	1.82 (1.56-2.13)	1.30(0.92-1.86)
Bronchitis	16.4	12.4	10.2	13.0	1.33 (1.14-1.56)	1.22 (1.04-1.42)	1.14(0.79-1.65)

CI: Confidence Interval

†Adjusted odds ratios (95% CI) were derived from logistic models. Reference category was self-report "No." Adjustment was made for number of vaccines received other than anthrax (0,1,...,5); gender (male vs. female); age in 1991 (<30 vs. ≥ 30 yrs); race (white vs. other); marital status (single vs. ever married); rank (officer or warrant vs. enlisted); branch of service (non-ground troops vs. ground troops); unit component (active duty vs. National Guard or Reserves); current alcohol use (within past 12 months); and current cigarette use (within past 12 months).

*Adjusted odds ratios (95% CI) for documented vaccination by DoD records relative to self-report "No" were derived through stratified Cochran-Mantel-Haenszel (1,5) analysis. Adjustment was made for variables that were correlated with both exposure (anthrax vaccine) and outcome (medical condition). These confounding factors included number of vaccines received other than anthrax, (≤ 2 vs ≥ 3); gender (male vs female); branch of service (non-ground troops vs. ground troops); unit component (active duty vs. National Guard or Reserves).

TABLE 4. Prevalence and adjusted odds ratios of selected self-reported severe symptoms among 11,441 Gulf War veterans according to self-report of anthrax vaccination; also for 352 Gulf War veterans for whom anthrax vaccination is documented in DoD records.

Symptoms	Self-Reported Anthrax Vaccination: Yes (N=4601)	Unknown (N=3361)	No (N=2975)	Documented DoD (N=352)	Adjusted Odds Ratio (95% CI) †: Anthrax Vaccination Yes†	Unknown†	DoD*
Joint aches or pain	21.8	16.8	9.7	16.5	2.05 (1.76-2.39)	1.76 (1.51-2.06)	1.50(1.09-2.10)
Runny nose	21.7	17.8	12.9	20.5	1.53 (1.30-1.76)	1.43 (1.24-1.64)	1.32(0.96-1.81)
Headaches	21.4	17.7	11.3	16.8	1.69 (1.46-1.96)	1.53 (1.32-1.77)	1.18(0.85-1.64)
Back pain/spasms	20.4	18.5	12.4	13.1	1.54 (1.34-1.78)	1.51 (1.31-1.74)	0.98(0.69-1.40)
Anxious, irritable or upset	19.2	15.1	8.2	15.0	2.02 (1.72-2.38)	1.75 (1.49-2.06)	1.46(1.03-2.07)
Excessive fatigue	18.8	13.4	7.1	14.3	2.19 (1.85-2.60)	1.83 (1.54-2.18)	1.62(1.14-2.31)
Sleep difficulty	18.3	13.8	7.6	15.1	2.04 (1.72-2.40)	1.71 (1.44-2.02)	1.57(1.11-2.21)
Awaken tired or worn out	17.8	13.8	7.8	14.0	1.86 (1.57-2.19)	1.62 (1.38-1.92)	1.30(0.93-1.81)
Been depressed or blue	15.4	11.8	6.7	12.1	1.94 (1.62-2.31)	1.65 (1.38-1.97)	1.43(0.99-2.06)
Reflux, heartburn, indigestion	14.8	11.9	6.7	12.0	1.93 (1.62-2.31)	1.72 (1.44-2.06)	1.65(1.13-2.43)

CI: Confidence Interval

†Adjusted odds ratios (95% CI) were derived from logistic models. Reference category was self-report "No." Adjustment was made for number of vaccines received other than anthrax (0,1,...,5); gender (male vs. female); age in 1991 (<30 vs. ≥ 30 yrs); race (white vs. other); marital status (single vs. ever married); rank (officer or warrant vs. enlisted); branch of service (non-ground troops vs. ground troops); unit component (active duty vs. National Guard or Reserves); current alcohol use (within past 12 months); and current cigarette use (within past 12 months).

*Adjusted odds ratios (95% CI) for documented vaccination by DoD records relative to self-report "No" were derived through stratified Cochran-Mantel-Haenszel (1,5) analysis. Adjustment was made for variables that were correlated with both exposure (anthrax vaccine) and outcome (severe symptom). These confounding factors included number of vaccines received other than anthrax, (≤ 2 vs ≥ 3); gender (male vs female); branch of service (non-ground troops vs. ground troops); unit component (active duty vs. National Guard or Reserves).

TABLE 5. Prevalence of disability, health care utilization, and selected medical conditions among 352 Gulf War veterans for whom anthrax vaccination records exist in DoD stratified by self-reported response to question on anthrax vaccination.

Indices/Conditions	Documented DoD N=352: Yes N=260	Unknown N=58	No N=34
Functional Impairment	30.3	13.8	14.7
Limitation of Employment	19.9	12.3	5.9
Clinic Visit	58.1	41.4	47.1
Hospitalization	10.0	8.6	5.9
Dermatitis	31.2	28.1	20.6
Gastritis	32.6	20.7	14.7
Arthritis	29.3	19.0	17.6
Frequent diarrhea	28.8	12.1	5.9
Hair Loss	17.1	17.2	8.8
Migraines	17.6	12.3	8.8
Lumbago	14.5	17.2	8.8
Bronchitis	14.6	6.9	11.8

Significance probability for Wilcoxon signed ranks test, p < .01 (2-tailed). (17)

TABLE 6. Prevalence of severe symptoms among 352 Gulf War veterans for whom anthrax vaccination records exist in DoD stratified by self-reported response to question on anthrax vaccination.

Symptoms	Documented DoD N=352: Yes N=260	Unknown N=58	No N=34
Joint aches pain	17.7	12.1	15.2
Runny nose	22.8	10.3	20.6
Headaches	18.1	17.5	5.9
Back pain/spasms	14.2	12.1	5.9
Anxious, irritable or upset	18.0	8.6	2.9
Excessive fatigue	17.4	6.9	2.9
Sleep difficulty	17.8	8.6	5.9
Awaken tired or worn out	17.1	6.9	2.9
Been depressed or blue	14.2	6.9	5.9
Reflux, heartburn, indigestion	12.0	10.5	14.7

Significance probability for Wilcoxon signed ranks test, p < .01 (2-tailed). (17)

CONCLUSIONS

- This survey data along with the DoD list of Gulf War veterans who received anthrax vaccine provide an opportunity to evaluate the long-term health consequences of anthrax vaccination.
- Those who reported exposure to anthrax vaccination do express more adverse health outcomes than those who reported no anthrax vaccination.
- The possibility of a reporting bias in exposure history should be carefully considered when one evaluates the health consequences of anthrax vaccination based on self-reported vaccination data.

Presentation 15 – Jack Melling

Current/Future Anthrax Vaccine Studies

Jack Melling

Program Details

NIH Program

- **rPA cloned into delta Sterne *B. anthracis***
- **Currently in phase I**
- **Contractors Vaxgen/Battelle**

NIH Program

- **rPA cloned into *E. coli***
- **Currently in phase I**
- **Contractors Avecia/DSTL**

CDC Program

- **Study on AVA to support change in dose regimen**
- **1560 human volunteers**
- **Due to report September 04**

DOD/JVAP Program

- **rPA cloned into *E.coli***
- **Contractor DVC**
- **Currently in phase I (04/03 – 12/05)**

ID Biomed -Canada

- **Cloned rPA**
- **Intranasal vaccine under development**

Presentation 16 – Lea Steele

Research Advisory Committee on Gulf War Veterans' Illnesses

Committee Work Plan

Jim Binns
Lea Steele

RAC Committee Work Plan: Topics for Discussion

1. Meeting Schedule
2. Regular Content of Committee Meetings
3. Specific Topics for 2004 Meetings and Future Reports
4. Communications
5. Reports
6. Staff Activities

RAC Committee Work Plan

- **Meeting Schedule**
  - 3 times/year: ~February, ~June, ~October

RAC Committee Work Plan

- Regular Content of Committee Meetings
  - "Mini-symposiums" on scheduled topics
  - Breaking news related to GWI
  - Update on VA research and admin. activities related to GWI
  - Update on other federal activities related to GWI
  - Overview of GWI-related research published since prior meeting
  - Discuss recommendations, status of prior recommendations
  - Other issues/topics raised by committee members
  - Public comments

RAC Committee Work Plan

- **Topics for 2004 RAC Meetings and Future Reports**
  - Research re: exposures of concern
  - Systematic consideration of possible treatments for GWI

RAC Committee Work Plan: Topics for 2004 Meetings and Future Reports

- **February, 2004, Meeting**
  - Depleted uranium
  - Infectious diseases
    Immunological research related to GWI
    Additional vaccine issues possibly related to GWI (multiple vaccines, adjuvants, etc.)
  - ??Unexplained pneumonia, other health concerns associated with Operation Iraqi Freedom??
  - Reports on individual examples of GWI treatments

RAC Committee Work Plan: Topics for 2004 Meetings and Future Reports

- **June, 2004, Meeting**
  - Relationship of GWI to other conditions (e.g. neurological conditions, CFS, MCS, FMS, etc)
  - Overview of biological abnormalities documented in GWI, other unexplained syndromes
  - Overview of treatments used to treat "well-established" medical conditions with similarities to GWI
  - Overview of research on treatments for unexplained illnesses
  - Reports from clinicians who regularly treat veterans with Gulf War illnesses
  - Presentations/discussions of untried treatments that might hold promise for GWI (with invited experts)

RAC Committee Work Plan: Topics for 2004 Meetings and Future Reports

- October, 2004, Meeting
  - Oil well fires
    Other hydrocarbon exposures of potential concern (e.g. jet fuel, tent heaters, etc.)
    CARC paint
    Sand
    Respiratory conditions in Gulf War veterans
  - Other exposures of possible concern
  - Overview of research evidence re: association of exposures with GWI
  - Reports on individual examples of GWI treatments

RAC Committee Work Plan: Communications

- Committee Members
  - Email major GWI news as it comes out
  - GWI/RAC updates sent out biweekly or monthly
    Abstracts/complete articles of recently-published research
    Government publications or activities related to GWI
    News articles on GWI
    Committee activities, business

RAC Committee Work Plan: Communications

- Public
  - Maintain on website
    Meeting information: agenda, minutes, etc.
    Committee documents and briefs
    Info on/links to GWI-related research funding opportunities
    Info on/links to studies that are recruiting Gulf veteran subjects
  - Respond to correspondence, phone inquiries, media requests

RAC Committee Work Plan: Reports

- Frequency of Regular Reports
- Upcoming 2004 Report and Recommendations
  - Basic structure similar to Executive Summary. Will also include key points from RAC interim report, elaboration of scientific details in appendices.
  - Targeted timeline for completion:

Dec. 15	Draft to committee members for review
Jan. 11	Final draft to committee members for approval
Jan. 18	Report to Secretary

  - Public release of report in late January/early February
  - Results briefed to federal government officials, others

RAC Committee Work Plan: Staff Activities

1. Monitor, review scientific research
2. Draft RAC written products
3. Communications with government agencies, media, etc.
4. Communications with the public
5. Committee meeting support
6. Administrative activities