Research Advisory Committee on Gulf War Veterans' Illnesses

December 12-13, 2005 Committee Meeting Minutes

U.S. Department of Veterans Affairs
810 Vermont Avenue, N.W., Room 230
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 December 12-13, 2005, 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

Table of Contents

Attendance Record

Members of the Committee
James H. Binns, Chairman
Beatrice Golomb
Joel Graves
Robert W. Haley
Marguerite Knox
William J. Meggs
James P. O'Callaghan
Steve Robinson
Steve Smithson
Lea Steele

Committee Staff
Laura Palmer
Barbara LaClair

Guest Speakers
William Goldberg
Joel Kupersmith
Jonathan Gurland
Michelle Jones

Abbreviations

AChE	Acetylcholinesterase
AFIP	US Armed Forces Institute of Pathology
ALS	Amyotrophic Lateral Sclerosis
CDC	Centers of Disease Control
CFS	Chronic Fatigue Syndrome
CMI	Chronic multisymptom illness
CRADO	Chief Research and Development Officer (VA)
DoD	US Department of Defense
DU	Depleted uranium
EPA	US Environmental Protection Agency
FACA	Federal Advisory Committee Act
FY	Fiscal year
GAO	US Government Accountability Office
GWVIS	Gulf War Veteran Information System (VA)
HPA	Hypothalamic pituitary adrenal axis
IOM	Institute of Medicine
IRB	Institutional Review Board
MAVERIC	Massachusetts Veterans Epidemiology Research and Information Center
MoD	Ministry of Defence (UK)
MS	Multiple sclerosis
NIH	National Institutes of Health
NIOSH	National Institute of Occupational Safety and Health
NGWRC	National Gulf War Resource Center
OEF	Operation Enduring Freedom
OIF	Operation Iraqi Freedom
ORD	Office of Research and Development (VA)
OSAGWI	Office of the Special Assistant for Gulf War Illnesses (DoD)
PB	Pyridostigmine bromide
PTSD	Post traumatic stress disorder
RAC-GWVI	Research Advisory Committee on Gulf War Veterans' Illnesses
RFA	Request for applications
UK	United Kingdom
US	United States
USACHPPM	US Army Center for Health Promotion and Preventive Medicine
VA	US Department of Veterans Affairs
VBA	Veteran's Benefits Administration
VHI	Veterans' Health Initiative (VA instructional program for physicians)
VISN	Veterans Integrated Service Network (VA)

WRIISC War-Related Illness and Injury Study Center (VA)

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

US Department of Veterans Affairs
810 Vermont Ave., N.W. (Room 230) Washington, D.C.

Agenda
Monday, December 12, 2005

8:00 – 8:30	Informal gathering, coffee	
8:30 – 9:00	Meeting called to order Welcome, opening remarks, introduction of new members	Mr. Jim Binns, Chairman
9:00 – 10:00	Federal Advisory Committee ethics training	VA staff
10:00 – 10:15	Break	
10:15 – 11:15	Overview of exposures and health conditions reported by countries who served in 1990-1991 Gulf War Allied Coalition	Ms. Barbara LaClair, RAC-GWVI staff
11:15 – 12:00	Review/discussion of topics considered in 2004-2005	Dr. Lea Steele
12:00 – 1:00	Lunch	
1:00 – 2:45	Review/discussion of topics considered in 2004-2005	Dr. Lea Steele
2:45 – 3:00	Break	
3:00 – 4:30	Overview and summary: Wartime exposures in relation to chronic health problems in Gulf War veterans	Dr. Lea Steele
4:30 – 5:00	Public comment period	
5:00	Adjourn for the day	

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

US Department of Veterans Affairs
810 Vermont Ave., N.W. (Room 230) Washington, D.C.

Agenda
Tuesday, December 13, 2005

8:00 – 8:30	Informal gathering, coffee	
8:30	Meeting called to order	Mr. Jim Binns, Chairman
8:30 – 9:00	VA Office of Research and Development report on Gulf War-related funding announcements	Dr. Joel Kupersmith. VA Chief Research and Development Officer
9:00 – 10:00	VA Office of Research and Development report on recently-funded Gulf War research studies and VA Gulf War research portfolio	Dr. Bill Goldberg, VA Gulf War Illness Portfolio Manager
10:00 – 10:15	Break	
10:15 – 11:00	Status of VA Gulf War research program in relation to 2004 RAC recommendations	Dr. Bill Goldberg
11:00 – 12:00	2006 RAC Report	Dr. Lea Steele
12:00 – 1:00	Lunch	
1:00 – 1:30	Committee business	Mr. Jim Binns Dr. Lea Steele
1:30 – 2:00	Public comment period	
2:00	Adjourn	

Drs. Carrolee Barlow, Floyd Bloom, Daniel Clauw, Mary Nettleman and Hugh Tilson, who were appointed to the Committee on October 26, 2005, were not able to be present for this meeting, which had been scheduled prior to their appointments.

Welcome, introductions, and opening remarks

James H. Binns, Jr., Chairman

Chairman James Binns called the meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses (RAC-GWVI) to order at 8:38 a.m. He thanked everyone for attending.

Chairman Binns stated that there were two major purposes of this meeting: (1) to review and discuss information presented to the Committee over the past two years in preparation for the Committee's 2006 report; and (2) to obtain information from the Department of Veterans Affairs' (VA) Office of Research and Development (ORD) on the outcome of the FY2005 Gulf War Illness Request for Applications (RFA), along with FY2006 plans and initiatives.

Chairman Binns noted that the Committee had received notebooks with the 2004-2005 meeting minutes. He expressed his appreciation of the work Dr. Steele, Ms. Palmer and Ms. LaClair had done in organizing the meetings for the past two years. He noted that these meetings had brought together experts representing all points of view on the subject topics, creating not only an opportunity to listen to these researchers, but also bring them together to talk with each other. He also expressed his appreciation at seeing VA ORD now fully participating in the Committee's discussions. He noted that it was beneficial for all involved to hear the same scientific data.

Chairman Binns introduced Dr. Joseph Francis, VA's new Acting Deputy Chief Research and Development Officer (CRADO). Dr. Francis provided the Committee with background information about himself. He is a general internist and geriatrician with a broad research background. He has been involved in health care administration for the past ten years, was Chief Medical Officer for one of VA's Veteran Integrated Service Networks (VISN) and was Director of Education and Research for a large private health system. Besides acting as Deputy CRADO, Dr. Francis is currently Director of VA's Quality Enhancement Research Initiative.

Chairman Binns stated that six new Committee members had been appointed by Secretary Nicholson on October 26, 2005. Due to the short notice, several (Drs. Carrolee Barlow, Floyd Bloom, Daniel Clauw, Mary Nettleman and Hugh Tilson) were not able to attend this pre-scheduled meeting. He stated that they would be involved in determining the Committee's 2006 meeting schedule.

Chairman Binns then introduced Dr. Jim O'Callaghan, who was appointed to the Committee in October. Dr. O'Callaghan is a Centers for Disease Control and Prevention (CDC) Distinguished Consultant and the Head of the Molecular Neurotoxicology Laboratory in the Toxicology and Molecular Biology Branch of the Health Effects Laboratory Division at CDC and the National Institute of Occupational Safety and Health (NIOSH). He received his PhD in Pharmacology from Emory University, held four National Institutes of Health (NIH) fellowships, and has received over ten Distinguished Achievement Awards of the Environmental Protection Agency (EPA) and CDC. He was a guest investigator in Dr. Paul Greengard's laboratory at Rockefeller University, as well as being an Adjunct Professor at the University. He has authored over 100 peer-reviewed publications, presented over 150 invited lectures, and serves on the editorial boards of the journals of *Neurotoxicology* and *Neurotoxicology and Teratology*.

Dr. O'Callaghan stated that he was honored and delighted to join the Committee, and thanked Chairman Binns for his introduction. Dr. O'Callaghan indicated that he was a "lab guy", spending the majority of his career conducting basic research into the effects of chemicals on the nervous system. He commented that there was still much to learn about neurotoxicology, and he was focusing on mechanisms and associated dysfunction at the molecular level. He was involved with CDC's "Research to Practice" program, which translates the practical aspects of his bench work to actual real-world application.

The Committee and staff introduced themselves to Dr. O'Callaghan and the audience.

Federal Advisory Committee ethics training

Mr. Jonathan Gurland and Ms. Michelle Jones, who are with VA's Office of General Counsel, provided training presentations to the Committee on the Federal Advisory Committee Act (FACA) and ethical rules which pertained to them as federal advisory committee members. Mr. Gurland and Ms. Jones provided members with two documents: (1) a brochure entitled "The Federal Advisory Committee Act: An Overview; and (2) a handout entitled "Ethics Rules for Advisory Committee Members Who Are Special Government Employees."

Chairman Binns thanked Mr. Gurland and Ms. Jones for their presentations.

The meeting adjourned at 9:59 a.m. for a break.

The meeting reconvened at 10:21 a.m.

Chairman Binns noted that there would be a change in the following day's (December 13th) schedule, in which the Committee would be working through the lunch hour so as to adjourn at 1:00 p.m.

Dr. Steele outlined the meeting's schedule and explained that the main focus of this meeting was to review materials presented to the Committee on topics covered over the past two years and to discuss findings and recommendations for the Committee's 2006 report. She noted, however, that the meeting would begin with Ms. LaClair's presentation of additional information for the Committee to consider in its review process. She said that when discussing Gulf War illnesses, questions often arise regarding the health of veterans from other Allied Coalition countries, as well as local populations. She stated that Ms. LaClair's presentation would help address some of these questions. She noted that this information approached Gulf War illness questions from an ecological perspective, analyzing patterns of exposures and health outcomes by country, and that this material might assist the Committee in describing the "big picture" of what exposures may be contributing to Gulf War illnesses.

Overview of Exposures and Health Conditions Reported by Countries who Served in the 1990-1991 Gulf War Allied Coalition

Barbara J. LaClair, MHA
Research Health Scientist, Research Advisory Committee on Gulf War Veterans' Illnesses

Ms. LaClair presented an overview of available information related to exposures and health conditions experienced by 1990-1991 Gulf War veterans from other nations, including the United Kingdom (UK), Canada, Australia, France, Czechoslovakia, and the Arab Coalition. (See Appendix A - Presentation 1.)

Dr. Robert Haley stated that it was interesting looking at this issue at this point in time. He noted that the similarity between the United States (US) and UK experiences were striking. Ms. LaClair agreed, and noted that there were striking similarities for both the troop exposures and health symptoms. She stated that one of the frustrations in doing this analysis was that the data from the various countries were not always comparable. Thus, a liberal approach was required to compare and interpret this information.

Dr. Haley asked whether any other country, besides the US and UK, had reported odds ratios for exposures in relation to defined multisymptom conditions. He stated that he had seen eight US studies and one UK study that had attempted to do odds ratios for risk factors. Dr. Steele noted that the Australian study had used defined symptom groupings and scores, and used adjusted ratios of the means for symptom scores in relation to exposures. Ms. LaClair stated that the Canadian study had used combined symptom groups as health outcomes, and that Chronic Fatigue Syndrome (CFS) was one of these groups. She stated that the study had calculated prevalence odds ratios in relation to grouped exposures but she had not included those in her presentation because they had not been presented in a way that was comparable to results from other countries. Dr. Steele noted that absolute rates of these defined outcomes in the Canadian study could be compared with the absolute rates in the Iowa Study.

Dr. Steele thanked Dr. Francis O'Donnell, with the Department of Defense's (DoD) Deployment Health Support Directorate, for helping Committee staff obtain a translated copy of the French Gulf War veterans study. She indicated that they had hoped the study would provide information about the prevalence of symptoms among French veterans. However, the broad nature of symptom questions used in this study and lack of a comparison group made the French results difficult to interpret.

Dr. Beatrice Golomb commented that attributable risk could be calculated using the odds ratio or risk ratio and rate of exposure to determine the amount of excess illness in Gulf War veterans related to a particular exposure.

Dr. Bill Meggs concurred that it was difficult to draw conclusions from this type of data, particularly for the countries who deployed small numbers of troops. However, he found it interesting that Denmark had a decreased exposure to pesticides and nerve agents and also lower neurological and musculoskeletal symptoms. He stated that conclusions could not be drawn from this, but that it was suggestive. Ms. LaClair agreed that this approach was nonquantitative and ecological. Dr. Golomb noted it could be made somewhat quantitative by looking at low and high estimates of odd ratios from different papers and using the best estimates from the deployed and nondeployed groups.

Ms. Marguerite Knox noted that Saudi Arabia had the third largest number of troops with 45,000 deployed. The Saudi study reported on only addressed 15,000 from the National Guard. Ms. LaClair stated that National Guard troops who had participated in combat had been compared to troops who had been in the Riyadh area.

Dr. Haley inquired about the Harvard School of Public Health study looking at the Kuwait population. Dr. Steele stated that this study hadn't been published yet. She indicated that the researchers have identified a 30% increase in mortality among Kuwaitis over the age of 50 who remained in the country during the war, compared to those who left Kuwait during the war. The researchers did not know the reason for this increase but that did not think it could be attributed exclusively to the oil well fires. They believed it may be due to the stress of being in the war zone. Dr. Steele stated that the study would also investigate health outcomes in the younger Kuwaiti population, and would obtain information about rates of chronic multisymptom illness (CMI) in this group.

Dr. Steele also said that there was little scientific information regarding the health of other local populations. She noted that there were scattered studies done in Bahrain and Kuwait, usually clinical reports using hospitalization data. She noted that shortly after the war, there were claims that Kuwait had suffered a great amount of excess illness as a result of the war. However, when data were reanalyzed, it was found that the associations weren't as strong as initially claimed because Kuwaiti hospitalization rates had already been increasing before the war.

Chairman Binns thanked Ms. LaClair for pulling this information together for the Committee's review. He stated that he was struck by two things: (1) one exposure may not be the only cause, but rather a combination of these exposures may be more toxic; and (2) the amount and significance of exposure to nerve agents appears to still be a contested issue, whereas pesticide exposures were less contested, except perhaps with respect to the degree of exposure.

Ms. Knox commented on the discrepancy noted with regards to the use of pyridostigmine bromide (PB) pills. She stated that troops were issued these pills before the war, and the decision to use them was to be made by each unit's commander. However, in practice, many individuals took the tablets without a command order. Ms. LaClair stated that the exposure data were self-reported, which could account for any usage or nonusage without regard to command decision.

RAC 2006 Report: Overview of Material Considered in 2004-2005; Review of Information Presented on Depleted Uranium

Lea Steele, PhD
Scientific Director, Research Advisory Committee on Gulf War Veterans' Illnesses

Dr. Steele presented an overview of topics reviewed by the Committee in 2004-2005 and the types of information that would be included in the 2006 Committee report. She then provided a summary of scientific information presented to the Committee that related to possible health effects of depleted uranium (DU) exposure. (See Appendix A – Presentation 2.) Information reviewed included presentations related to DU exposure levels in the Gulf War, animal studies evaluating the effects of DU, and information from epidemiologic studies relating DU exposure to the health of Gulf War veterans. A variety of presentations made to the Committee in 2004-2005 were referenced, including those provided by Mr. Al Marshall, Dr. Mark Melanson, Ms. Mary Ann Parkhurst, Dr. Terry Pellmar, Dr. Wayne Briner, Dr. David Barber, Dr. Johnnye Lewis, Dr. Melissa McDiarmid, and earlier presentations by Dr. Steele. The Committee then discussed unanswered questions in relation to DU and the health of Gulf War veterans, and recommendations to be included in the Committee report. .

Dr. Golomb inquired about the possibility of asking Dr. Han Kang to include a DU exposure question in his Persian Gulf War veterans' longitudinal study. She also indicated that without a better sense of where DU fit in the spectrum of things potentially related to veterans' health problems, it would be hard to say what priority this research should have overall, but thought that it was very important to the subset of veterans with high-level exposures. This should be balanced against research priorities for the broader group of veterans with multisymptom problems. Dr. Steele stated that the animal research in this area had been informative and that before she had seen the DU neurotoxicology studies it was hard to imagine a biological rationale for potential relationships between DU exposure and chronic multisymptom illness. These studies had demonstrated that DU had similarities in uptake and kinetic properties to other heavy metals and was potentially associated with brain and behavioral effects. .Drs. Golomb and Steele agreed that more data were needed.

Dr. Haley asked whether Dr. Kang's survey had asked questions regarding DU exposure. Dr. Golomb commented that DU questions had not been asked in the 1999 study. Dr. Haley stated that one of the problems with early surveys was that researchers used the wrong approach when drafting questions pertaining to DU. He stated that the researchers were thinking about the possible low-level radiation effects, not necessarily the possible chemical toxicity and inhalation/aerosolization of DU. He stated that someone needed to think through the "right" DU questions to ask on these surveys. Dr. Steele stated that the National Gulf War Resource Center (NGWRC) had developed several straightforward questions pertaining to veterans' activity and behaviors that were indicative of DU exposure in the field. She used these questions on one of her studies. Committee members discussed the Camp Doha fire, an incident that involved troop exposure to burning vehicles and munitions containing DU.

Mr. Steve Smithson asked if it would be worthwhile to make recommendations regarding Dr. McDiarmid's DU study at the Baltimore VA. Dr. Steele indicated that the Committee might consider recommending that the Baltimore study be expanded to include more exposed veterans and additional health outcomes. Another possibility was suggesting that a separate study be conducted to identify veterans with Level 2 exposures for comparison to veterans with no DU exposure. Dr. Steele noted that the local population may have also experienced lower-level DU exposures and that soldiers in the current war may have experienced similar exposures. Drs. Golomb and Haley noted that it would be difficult to tease out the effects of DU on the local population because there were so many different toxins in the area.

Dr. Meggs stated that better toxicodynamics and toxiokinetics studies could be conducted in this area. He noted Dr. Barber's findings that mice who had received single intramuscular injections of uranyl acetate continued to excrete uranium for 30 days, and those with implanted pellets excreted uranium indefinitely. He noted that not much was known about the health effects of inhalational exposure to DU. Dr. Steele said that Dr. Lewis had been the only one conducting inhalational studies on animals. She stated that Dr. McDiarmid may be assuming that because individuals with DU shrapnel did not exhibit measurable health effects, inhalational exposure would be expected to have even less health risk. Dr. Meggs stated it would be interesting to follow an individual with a high-dose inhalational exposure to see if DU had accumulated in the body.

Dr. O'Callaghan commented that in terms of metal neurotoxicity, findings such as Dr. Barber's that demonstrated that DU was retained in the brain and exhibited dose response effects were impressive. The brain doesn't like metals that aren't already there, and even if the metal is found at a very low level, there might still be brain damage. It is very typical to accumulate metals in the liver and kidney which can cause problems, but barely detectable levels of metals in the brain can cause substantial region-dependent damage. He noted that Dr. Barber's findings show distribution of uranium in different areas of the brain. He stated it was typical that even when metal levels are evenly distributed across brain areas, damage would vary by area due to the selective vulnerability of the brain cell types. He saw data on different DU levels by brain region, but not on differential effects of these exposures by brain region. Dr. Steele stated that Dr. Barber's group, who are continuing to study this issue, had considered this. She indicated that staff could talk to them about their findings on this matter.

Dr. O'Callaghan stated that it was very important to understand what brain regions are targeted and adversely affected in the long term so that neurological outcomes could be determined. Dr. Steele asked what damage outcomes would be expected if, as studies indicated, there was greater accumulation in the hippocampus and striatum. Dr. O'Callaghan stated that predictions might be learning and memory deficits, along with motor and cognitive deficits. He noted that, in neurotoxicology terms, it is common to see even distribution throughout the brain, but uneven effects. However, with data showing uneven distribution, one would want to get better pharmacokinetic and toxicokinetic data for these brain regions

to determine a variety of measures for adverse outcomes on the nervous system. He stated that there were many cases of devastating human neurotoxic exposures in which heavy metals were found in the urine, but low levels were detected in the brain. He said that finding detectable levels of uranium in the brains of lab animals was bad.

Dr. Golomb suggested that the potential relationship between acetylcholinesterase (AChE) inhibitors and DU exposures be investigated, considering there is evidence that AChE inhibitors may increase blood-brain barrier permeability. She noted that there was also evidence that multiple chemical sensitivity seemed to be associated with organophosphate exposures. This might also relate to findings that chronic inflammation in the nasal area could impair the "nose-brain barrier" function. She thought it possible that concurrent exposures might enhance the potential effects of DU. She noted also that there was evidence that aluminum exposure increased blood-brain barrier permeability and that other heavy metals like DU might have a similar effect. Dr. Steele mentioned Dr. Lewis' work demonstrating neurotoxic effects of inhaled manganese, and wondered if anyone in the Gulf War did not have nasal inflammation due to constant exposure to high levels of particulates in the region.

Diana Miller, an audience member and a neurotoxicologist with CDC, pointed out that the observed prolactin changes could be related to changes in dopamine levels in the brain as well as thyroid changes. These changes are seen with other heavy metals, like manganese.

Dr. Steele asked the Committee for its thoughts regarding recommendations related to DU and DU research. She referred to earlier ideas mentioned regarding expansion of the Baltimore cohort study and/or doing a separate cohort study of DU-exposed individuals, with a control group of nonexposed individuals. Dr. Golomb stated there was a need for epidemiologic data looking at the rates of chronic health problems, preferably with similar types of adjustment models as seen with the other exposure variables. Dr. Steele stated it was remarkable, after all this time, that there really wasn't much epidemiologic data on DU in relation to multisymptom illness.

Dr. Steele also asked about recommending animal research looking at the neurotoxic effect of DU. Dr. Golomb stated that she felt this was important, but wondered how important it was in terms of setting priorities for allocation of limited research funds. Chairman Binns stated that he shared Dr. Golomb's concern, because there was a limited research budget. However, he believed there were ways to address it in the report. First, one would wear their "scientist hat" and identify what is known, along with gaps and needs in this area of research. However, one would conclude by prioritizing these competing scientific needs in relationship to the needs of the majority of ill Gulf War veterans.

Dr. Meggs stated it might be beyond the Committee' province, but noted that DU was not going away. He stated that there would be subsequent exposures, which needed to be looked at by DoD beyond the Gulf War illnesses problem. He stated it appeared the percentage of veterans with significant DU exposure was too small to be a major factor in the 25% increase of symptoms across the categories seen in the first Gulf War. Regardless, he believed it was a very important toxin for the military to be "on top of" in the future.

Dr. Steele noted that the U.S. Armed Forces Institute of Pathology (AFIP) researchers had started to look at tungsten, due to the discussion of phasing in tungsten alloys and phasing out DU. She stated that some of the researchers have found that tungsten alloys are more problematic than DU. She also agreed that, if DU could cause chronic multisymptom illnesses, but required a substantial exposure to do this, it was unlikely that DU could be the primary cause of illnesses seen in the majority of Gulf War veterans. However, if it didn't require a substantial amount, simply requiring low-level DU exposure or DU as a cofactor with other exposures, then it might be a more plausible contributor to the problem. If low-level

DU exposure, alone, was a cause of multisymptom illnesses, we might expect greater indication that chronic multisymptom illnesses are a problem in the current war.

Dr. Haley inquired about the availability of reliable urinary assay methods for DU. Dr. Steele stated that this was a good question, and noted that the issue had been controversial. She stated that there were groups in Europe who claim that the 24-hour urine assay methods used by Dr. McDiarmid's group are not sensitive enough and believe there is a better assay. Dr. Haley stated that the Committee could recommend that a case control study be conducted, using a cohort of individuals with multisymptom illnesses or who have been exposed to DU. He noted that the most sensitive DU assay should be done. Dr. Steele suggested a variety of different assays could be tested. Dr. Haley agreed. He stated that the question needed an epidemiologic approach: Are people excreting DU, and if so, is this excretion related to their symptoms?

Dr. Steele opened the discussion to members of the audience.

Ms. Denise Nichols, an audience member and Gulf War veteran, suggested the Committee recommend looking at the DU DNA assay being conducted in Germany. She also suggested that, besides research concerns, the report should include clinical implications/recommendations that could be put into practice for Gulf War veterans being seen at VA. Suggestions might be to look at thyroid function or immune system changes. She stated that the research needed to be blended into clinical practice and that this was problem at VA. She agreed that the Committee should clearly identify scientific information needed with regards to DU.

The meeting adjourned at 12:34 p.m. for lunch.

The meeting reconvened at 1:34 p.m.

Review of Information Presented on Oil Well Fires and Petroleum Combustion Products

Lea Steele, PhD
Scientific Director, Research Advisory Committee on Gulf War Veterans' Illnesses

Dr. Steele presented a summary of the information presented in 2004-2005 on oil well fires and other petroleum combustion products. (See Appendix A – Presentation 3.) A number of presentations were referenced, including those made by Mr. Jeff Kirkpatrick, Mr. Warren Wortman, Dr. Jack Heller, Dr. David Cowan, Dr. Gary Friedman, and earlier presentations by Dr. Steele.

During the discussion of Dr. Friedman's presentation on oil well firefighters, Mr. Graves commented that the firefighters weren't living in the oil well fire plumes like the soldiers were. He stated that his unit was actually living in the plume for two weeks. Dr. Haley also noted that the oil well firefighters were a highly selective group of individuals. He stated that it would be expected that they would reflect a healthy worker effect. Dr. Steele agreed that the firefighters were not a perfect comparison group, but noted that it was rare to find any comparison group for isolated exposures encountered by Gulf War veterans and that she believed the information provided by this group was useful.

Following Dr. Steele's presentation, Ms. Knox suggested that one should go back and identify those individuals who are more prone to allergies and asthma. She stated that some soldiers' immune systems were stronger prior to deployment than others, and afforded them better protection to the various exposures experienced by the troops. She noted that individuals with asthma could be deployed to the

Gulf if their condition was under control. Dr. Steele stated that this was a good idea, but didn't know what post-exposure measurement might provide this information.

Dr. Meggs stated that Dr. Stewart Brooks (University of South Florida) had conducted a study that examined individuals who developed asthma following exposure to smoke or fumes. Dr. Brooks found that having an atopic disease was a major risk factor for developing asthma. Thus, if an individual had allergic rhinitis and was exposed to smoke or fumes, they were more likely to develop chronic rhinosinusitis or progress to becoming an asthmatic. He noted that most of the Gulf War studies looking at smoke exposures talked about asthma, but not chronic rhinitis. He stated that quality of life studies show that individuals with chronic rhinitis have a much lower quality of life compared to those with chronic asthma. Dr. Steele noted that the rate of chronic sinus congestion was commonly reported in both Gulf veterans and nondeployed veterans, so studies often didn't consider that symptom in connection with Gulf War illnesses. Dr. Meggs noted that there were well-documented associations between chronic rhinitis, depression, obesity, myalgias, etc.

Dr. Steele asked if Dr. Meggs knew of possible post-exposure measurements to determine an individual's susceptibility to inhaled substances. Dr. Meggs stated there were several ways to assess for present rhinitis, but wasn't aware of a way to assess for pre-exposure susceptibility. He noted these individuals' airways were considered "remodeled", which made them susceptible to an exposure.

Dr. Steele asked Mr. Graves if he could date the onset of his symptoms, or knew of anyone who could, from the time of his exposure to oil well fires. He stated that he couldn't say whether they developed in relation to exposure to oil fires alone any more than other exposures, e.g. pyridostigmine bromide (PB), by themselves.

Referring to Dr. Gregory Gray's research, Dr. Haley noted that, during the first year of their return, deployed Gulf War veterans had increased hospitalization rates for pulmonary problems. He said this was very important, because it was the time frame in which one would expect to see evidence of a large effect. He stated that this finding by Dr. Gray hadn't really been pursued further.

Dr. Meggs noted that Mr. Graves' comments about Gulf War soldiers being in a "toxic cocktail" needed to be kept in mind. He stated that the soldiers were exposed to various other toxins that the oil well firefighters were not. He commented that it could be the synergistic effect of these exposure combinations that explained why soldiers' health was affected, but not that of oil well firefighters. Dr. Steele agreed and stated that animal research examining the combination of smoke with other exposures was possible but that previous studies of combinations of exposures had not included oil fire smoke. .

Dr. Golomb stated there was a need to determine the apparent independent associations, and then look at subsets of exposures. Dr. Steele indicated that she would be presenting data on this later.

Dr. Steele opened the discussion to comments from the members of the audience.

Ms. Nichols suggested there were two sources of data regarding oil well fire exposure. These included: (1) Air Force evacuation records; and (2) Registry data collected upon return from the Gulf War. She stated that pulmonary function tests were conducted on returning soldiers. She noted that some of these troops had had pulmonary function tests before deployment to the Gulf. Dr. Steele stated that there were a couple of studies examining the pulmonary function of deployed and non-deployed Gulf war veterans. These studies had found no difference between the two groups. She stated that one unanswered question, however, was whether pulmonary function was different in veterans reporting chronic multisymptom illnesses.

Review of Information Presented on Vaccines

Lea Steele, PhD
Scientific Director, Research Advisory Committee on Gulf War Veterans' Illnesses

Dr. Steele presented a summary of information presented to the Committee related to the effects of vaccines. (See Appendix A – Presentation 4.) A number of presentations were referenced, including those made by Dr. Jack Melling, Dr. Beatrice Golomb, Dr. John Grabenstein, Dr. Phillip Pittman, Dr. Ya Fang Liu, Dr. Clare Mahan, and earlier presentations by Dr. Steele.

During the presentation, Dr. Haley voiced a concern about the credibility of government vaccine studies. Dr. Golomb stated that reported adverse effects from the anthrax vaccine were about .005%, whereas the actual rate was determined to be 10^4 higher with follow-up. She also noted that a recent newspaper article series described the underreporting of hospitalization rates among those receiving the anthrax vaccine. She stated that officials had reported 100 such hospitalizations, but the newspaper reporter had discovered there actually were 20,000 such hospitalizations. Dr. Haley stated that, out of all the subjects considered by the Committee, this area of research appeared to be censored most severely.

Dr. Steele asked how the Committee should address this issue in the report. Dr. Golomb suggested that the Committee point out the repeated objective discrepancies, and that the evidence seemed to contravene the published findings. She stated that there was no need to speculate about intent.

Ms. Knox noted that the anthrax vaccine received by troops in 1990-1991 was different than the current anthrax vaccine. She noted that the studies looking at the old vaccine found fewer side effects. It was suggested that more recent studies were not comparing "apples with apples." Dr. Meggs also noted that none of the studies looked at contributing effects of other exposures in relation to vaccines. Dr. Steele noted the Committee's discussion with Dr. John Grabenstein in April 2005, and the Committee's concern regarding the conclusions drawn from his group's work concerning hospitalization rates due to adverse vaccine effects.

During the discussion about squalene adjuvant in vaccines, Dr. Steele reported that Dr. Carl Alving's group was conducting a study that looked at whether ill Gulf War veterans had elevated squalene antibodies in comparison with healthy Gulf War veterans. She stated that the funding for this study had run out, but that the researchers were slowly, on their own time, trying to finish the work. She stated the staff would find out the status of this research before the Committee's report was issued. Discussion occurred about the differing assays used by Dr. Alving's and Dr. Pam Asa's groups. Dr. Golomb stated that Dr. Alving's group had published criticisms about Dr. Asa's findings before having data to support their opposing viewpoint. This created a conflict between the groups, and might result in a group's desire to reach a certain finding. Dr. Steele stated that Gary Matsumoto addressed this conflict in his book, *Vaccine A*. Dr. Haley suggested the need for a case control study conducted by an independent third party, which looked at the differing assays, along with vaccinated/non-vaccinated veterans. Drs. Golomb and Steele agreed that a blinded study conducted by a third party would be a good thing to do.

During the discussion about unanswered questions with regards to vaccines, Dr. Golomb commented that one of the Committee's central missions was to look at the excess illness occurring in Gulf War veterans. She stated that little was known about the illness complex from the current war. Dr. Steele noted that there was little animal research looking at the adverse effects of vaccines in combination with other exposures. Dr. Haley added that it might be beneficial to approach the question of vaccine effects from the opposite direction, e.g., specifically looking at the Rook hypothesis. Discussion occurred about looking for cytokine changes in ill Gulf War veterans. Dr. Haley thought it was worth summarizing this area of the literature in the Committee's report. He stated that concerns about multiple vaccinations had

generated this hypothesis. He noted that studies done in this area had been negative but that the hypothesis hadn't been ruled out completely. Dr. Golomb commented that the Rook hypothesis provided a departure point for public debate on something that should be addressed anyway, i.e., the role of cytokines in Gulf War illnesses. She suggested that the original departure point was not the central consideration, and that the larger issue—the role of cytokines—should be looked at systematically in light of current understanding, e.g. that there really isn't a pure Th1/Th2 dichotomy.

Dr. Golomb commented that there had been a couple of studies showing similar interleukin changes. Dr. Haley stated that the report should summarize these findings, since they provide the "other side of the coin" with regards to immunizations. Dr. Steele stated that different immune perturbations had been detected in different studies utilizing different methods and Dr. Golomb added that different exposures would be expected to lead to different cytokine shifts. Dr. Haley stated that, underlying all of this, was the use of different case definitions, which muddied things further. Dr. Steele agreed, and noted that the Peakman study may have been the strongest in terms of laboratory methodology, but that it had used a very nonspecific case definition.

Discussion occurred as to whether U.S. troops received the plague vaccine. Ms. Nichols stated that she had seen soldiers' records, showing the receipt of plague vaccine. Mr. Graves indicated that he believed that he had received the plague vaccine. Dr. Haley stated that, based on his understanding, the plague vaccine does not protect against aerosolized plague as would be encountered in a biowarfare situation. He stated that he had been told by General Blanck that plague vaccinations were not given to troops just because they were deploying to the Gulf War but that some troops routinely received the plague vaccine if they were being sent into an endemic area where they might be cutaneously exposed to infected animals. He said that British troops did receive this vaccination based simply on their deployment to the Gulf.

Ms. LaClair commented that the international data comparisons reviewed earlier in the day showed 22% of U.S. Gulf War veterans believed that they received the plague vaccine. Dr. Haley stated this might be attributed to misreporting by veterans, because many didn't know exactly what vaccinations they received. They simply knew they received vaccinations. Dr. Steele commented that it was difficult to find US studies of Gulf War veterans with complete shot records. She stated that the British had looked at UK veterans who had good records and found similar associations between vaccines and health outcomes among those with and without records. Dr. Golomb remembered that there were virtually no differences.

Review of Information Presented on Infectious Diseases

Lea Steele, PhD
Scientific Director, Research Advisory Committee on Gulf War Veterans' Illnesses

Dr. Steele presented a summary of information presented in 2004-2005 regarding the potential contribution of infectious diseases to chronic ill health in Gulf War veterans. (See Appendix A – Presentation 5.) A number of presentations were referenced, including those made by Dr. Alan Magill, Dr. Sam Donta, Dr. Quentin Deming, and earlier presentations by Dr. Steele.

During the discussion about Dr. Bourdette's study on leishmaniasis, Dr. Meggs stated that a follow-up study with more power was needed. Dr. Steele indicated that the assay used in the study had not been further developed. Dr. Haley commented that the group doing this study had had to contend with considerable challenges in moving this project forward but that they ultimately had not received additional funding and so had not continued this work. He stated that leishmaniasis was a good

hypothesis for Gulf War illnesses but that there was currently no way to diagnosis chronic leishmaniasis, unless one: (1) treated the individual and he or she got better; or (2) developed a more sensitive assay. However, the treatment for leishmaniasis (antimony) was toxic. Discussion followed concerning the difficulty of diagnosing viscerotropic leishmaniasis. Dr. Haley stated that the parasite "hides" in visceral cases, making it difficult to find, and that but it could even be difficult to accurately diagnosis an infected individual who was dying from hepatosplenomegaly. Chairman Binns asked what symptoms would be expected in a large infected group. Dr. Haley replied that there was thought to be an interaction between nutrition and the manner in which the disease presented itself. He stated that it wasn't known how a leishmaniasis epidemic would present in a group of well-nourished, healthy soldiers. He noted it probably would not result in hepatosplenomegaly and that it would be a difficult diagnosis, but the hypothesis should be tested.

Dr. Haley commented that he was part of a group, back in the late 1990's, that proposed a study that would treat a random sample of ill Gulf War veterans with amphotericin to see if they got better. He stated, without a more sensitive assay, this approach was the only way to determine if leishmaniasis was the cause of the veterans' health problems. Dr. Golomb was hesitant about this approach, but stated that, if there was any type of assay that could narrow the target population, it would improve the likelihood that true cases would be detected. Dr. Haley agreed, and wondered if Dr. Magill's group had been able to develop a better assay since he spoke to the Committee in February 2004.

Although she had been a co-author on the RAND infectious disease report (writing the chapter on mycoplasma), Dr. Golomb stated that she had reservations about the dismissal of the idea that an infectious disease was the problem faced by ill Gulf War veterans. She stated that she shared similar concerns about the possibility of ill veterans being affected by chronic leishmaniasis.

A discussion followed concerning various research studies that had been done on mycoplasma and Gulf War illnesses. Dr. Haley stated that there were two serological studies conducted by Dr. Lo. Dr. Golomb noted that serological assays are insensitive to mycoplasma. Dr. Haley stated that, even if the test was insensitive because of mycoplasma's ability to evade the host immune system, there should still be a higher prevalence of antibodies related to infection. He thought that Dr. Vojdani's study had not been blinded and was open to question because it had been conducted in a laboratory generating revenue from the test and that similar concerns were attached to Dr. Nicholson's study. He thought that Dr. Donta's study had not had those types of issues but did not directly address the issue because they didn't have a control group. The most valid studies, in his opinion, were Dr. Lo's serological studies. Dr. Steele disagreed, stating that if serological studies were not expected to detect intracellular mycoplasma infections, Drs. Vojdani's, Nicholson's and Donta's findings point to a testable hypothesis. Dr. Haley acknowledged this but thought the hypothesis was still untested with existing evidence and that the serological studies couldn't be discounted. Also, because mycoplasma is ubiquitous in the environment, Dr. Haley pointed out that cross contamination was a problem with PCR tests. Dr. Golomb stated there was a low quality of evidence supporting this hypothesis, but the evidence remained suggestive that mycoplasma could be a marker. She stated that, in her opinion, the mycoplasma infection was more likely a consequence rather than the primary cause of Gulf War illness.

To answer the question, Dr. Haley suggested that Dr. Joel Bateman's lab, which in his opinion was the best one for this testing, could be asked to do an analysis of case and control samples collected under strict guidelines to reduce contamination. Dr. Steele pointed out the lab results from Dr. Bateman's lab for the VA study had also provided anomalous results. While he believed there was no rationale or evidence for the hypothesis, Dr. Haley stated that a study should be done to put the issue to rest. Dr. Golomb disagreed that there was no evidence, but agreed that this research would not be at the top of her priority list.

During the review of Dr. Hyman's antibiotic treatment study, Chairman Binns recalled the input of Mr. Harold Nelson, an ill veteran who had been treated by Dr. Hyman, who reported that his health and quality of life had been restored by this treatment. Dr. Haley stated that he had treated an individual who developed severe renal failure following this treatment.

The meeting adjourned at 3:36 p.m. for a break.

The meeting reconvened at 3:51 p.m.

Upon return, Mr. Graves presented a chart which reflected an approach he had developed for organizing the material being reviewed by the Committee. (See Appendix A – Presentation 6.) Chairman Binns expressed his appreciation for Mr. Graves' organizational flow chart. He hoped that this type of presentation would stimulate discussion regarding the types of questions that most needed addressing. Mr. Graves stated that the purpose of the flow chart was to narrow the focus of interest.

Wartime Exposures in Relation to Gulf War Illnesses: Summary of the Evidence

Lea Steele, PhD
Scientific Director, Research Advisory Committee on Gulf War Veterans' Illnesses

Dr. Steele provided a presentation summarizing and comparing the evidence related to possible associations between the multisymptom illnesses affecting Gulf War veterans and Gulf War exposures, including psychological stressors. (See Appendix A – Presentation 7.) The presentation drew attention to differences between results of epidemiologic studies that did and did not analyze data in a way that controlled for confounding introduced by concurrent exposures. Using results from her own research, she illustrated how studies that did not apply appropriate statistical methods invariably found that almost all exposures appeared to cause Gulf War illnesses.

Mr. Robinson stated that DoD's Office of the Special Assistant for Gulf War Illnesses (OSAGWI) had a staff of database managers who took reports from Gulf War veterans, and asked about exposures similar to those identified by Dr. Steele. He believed that over 75,000 veterans were interviewed, and the information collected was used to direct OSAGWI's focus areas. Dr. Steele noted there was also a large amount of data collected by Dr. Han Kang's survey, which had a sample size of approximately 20,000. She stated, however, that Dr. Kang's analyses hadn't compared risk factors between sick and healthy veterans. Mr. Robinson asked if Dr. Kang's data was original, or based upon the information collected by OSAGWI. Dr. Steele stated that the data had been collected specifically for Dr. Kang's project. Because these data had been collected from a representative sample of Gulf War veterans, she stated that they would be more appropriate for research studies than the OSAGWI data.

Mr. Graves stated that he understood Dr. Steele to be saying that Gulf War illness may have been caused by a multi-combination of exposures. Dr. Steele agreed, noting, however, that in some studies, some exposures may only appear to be risk factors because they were linked to another exposure. Mr. Graves stated that he had long thought that PB and organophosphates may have caused Gulf War illness. Dr. Steele stated that this might be true for some people, but that different exposures and combinations might have affected different people in different ways. She noted that this was complicated question, and taking an overly simplistic approach could miss finding the answers.

Dr. Golomb stated that odds ratios and risk ratios are very important, but don't explain everything. If one had a rare, but powerful, exposure, it will be a very strong risk factor. However, it will have a low

attributable risk. Dr. Steele agreed, noting an example of this could be flea collars. Dr. Golomb stated that, in order to find the answer to this question, one would have to look at the differences in exposures and combine these with odd ratios. Dr. Steele stated that this was currently being examined, and attributable risks might be calculated if the necessary data are available.

Chairman Binns asked Colonel Frank O'Donnell, an audience member and staff member for DoD's Deployment Health Support Directorate, if DoD had changed the pesticide directives given to troops in the Gulf today versus that given in 1990-1991. Dr. O'Donnell stated that he was unaware of any change in those directives. He stated that both DEET and permethrin are being used. He stated that the problem that arose in the first Gulf War was the uncontrolled use of these pesticides. Dr. Haley asked if the high potency of DEET (75% in ethanol) was phased out. Dr. O'Donnell stated that this had been changed, noting that the current mixture ratio was 33% DEET. Dr. Steele noted the overuse of personal pesticides by 1990-1991 troops. Mr. Robinson stated that there was currently an emphasis on preventing the overlapping of pesticide spraying.

During Dr. Steele's preliminary summary of the evidence, Dr. Golomb questioned the animal studies pertaining to stress. She noted that researchers typically subjected animals to a physical condition, e.g. cold water, and called this "stress." Dr. Steele noted that the experimental physical exposures were never exactly like the conditions in the Gulf War. Dr. Golomb stated that the researchers had various concepts of stress, noting that Dr. Nisenbaum's study had referred to taking PB as "stress." Dr. Golomb commented that subjecting animals to cold water tests was not a pure psychological stress.

Dr. Diane Miller, an audience member and CDC neurotoxicologist, commented that this was the hypothetical constant of this type of research. She stated that researchers basically make manipulations and look at certain end points, e.g., looking at the hypothalamic pituitary adrenal axis (HPA) axis then determining if there is an increase in steroid levels. She noted that one does get into a problem by using the term "stress" in this type of research. Dr. Steele agreed, and wondered if it was valuable to make overly general statements about research findings in relation to any of the exposure questions. For example, psychological or physical stress in humans can cause acute symptoms and can also be associated with chronic symptoms among those affected by psychiatric illness such as PTSD. But it is unknown whether individuals exposed to potentially traumatic stressors who do not develop psychiatric illness have an increased rate of symptoms afterwards.

Mr. Robinson asked for clarification as to how the data presented on psychological stressors compare to clinical diagnosis data. Dr. Steele stated that they really relate to two separate questions. First, did psychological stressors during the Gulf War cause soldiers to become ill with chronic multisymptom illnesses? Second, upon return, what proportion of veterans developed a diagnosable psychiatric condition such as PTSD? Both questions are important. Chairman Binns noted that the general evidence on stress that had been referred to addressed a more theoretical question. i.e., can stressful exposures cause these kinds of symptoms? He stated that the data provided previously looked directly at the ill veteran population to determine if there was an association. This is where the psychological stressors did not relate, while theoretically they could relate.

Dr. Golomb noted that she was working on a similar project, and was seeing the same pattern with pesticides and PB being the most significant, followed by chemical warfare agents. Drs. Steele and Golomb discussed the methodology being utilized by Dr. Golomb in her project. Dr. Steele noted that unadjusted results were of limited use. Dr. Haley stated that the bar needed to be raised for the quality of future studies. Dr. Golomb stated that the report should make it clear that one should not use the modeling approach used by the Naval Health Research Center study, in which adjustment models included all exposures variables. Dr. Haley agreed, noting these approaches were two extremes that were

both misleading. Dr. Steele stated that, unfortunately, if studies utilizing these two extremes were discarded, there weren't many studies left. However, if concerns about confounding aren't adequately addressed, study results are questionable and generally indicate that everything causes Gulf War illness which, she noted, does not make sense.

Dr. Meggs commented that the day's presentations were a wonderfully clear and objective distillation of the literature in this area.

Chairman Binns asked Dr. O'Callaghan for his initial reaction, as a new Committee member, to the information presented that day. Dr. O'Callaghan stated that the most important point was making sure the appropriate research methods were being used. Studies using faulty methods were just wasting time. He found this to be a key point underlying the day's presentations and discussion. Dr. Steele noted that Dr. O'Callaghan would be able to provide insight into the best methods in laboratory science research. Dr. O'Callaghan acknowledged that expertise was needed in both laboratory and epidemiology methods in order to determine whether data and subsequent findings were valid or not.

Mr. Robinson stated it was critical to ask the questions that needed to be asked, and then answer them. He commented that ruling out certain things, while ruling in others, was vitally important, especially in determining the direction of research and finding treatments. He believed this review and approach was a great service for Gulf War veterans, and, once the information was teased out, would help veterans focus too. He stated that this type of review had never been done, and was great work.

Dr. Steele stated that the Committee's next report would draw from these conclusions and point out some of these findings.

Mr. Robinson asked whether the report would also indicate areas that needed further study because data are lacking. Dr. Steele stated that this was an important point and would be addressed in the report. For example, she noted that there is little research looking at DU exposure in relation to multisymptom illness. She stated that a basic epidemiological study was needed to provide information about Gulf War illness and DU. Once this information is available, additional decisions could be made concerning next steps.

Chairman Binns commented that, one-and-half years ago, he would have been in the camp that would be questioning the relevance of "rehashing" all of this information again. His views had changed, and he was pleasantly surprised by the amount of hard information collected and derived to answer these questions. He credited Dr. Steele with developing these insights.

Public Comment – Day 1

Ms. Denise Nichols addressed the Committee. She asked that the Committee consider holding at least one 2006 meeting outside of Washington, DC. She stated that many veterans were not able to attend the meetings and suggested coordinating the Committee meeting with a medical meeting to get interest from other researchers. She hoped that the Committee's next report would address clinical management implications. She also hoped that the report would be very specific as to the types of research needed in order to educate and direct researchers applying for the grant money. She also asked that the Committee ask the Veteran's Benefits Administration (VBA) to collect information about immune and endocrine disorders being seen in Gulf War veterans.

The meeting adjourned for the day at 5:11 p.m.

The meeting reconvened on Tuesday, December 13, 2005, at 8:35 a.m.

VA Office of Research and Development Report

Joel Kupersmith, M.D.
Chief Research and Development Officer, Department of Veterans Affairs

Dr. Kupersmith gave an overview of VA research, the regulations that guide this research, and the progress made by VA in Gulf War illnesses research over the previous three months. (See Appendix A-Presentation 8.)

Dr. Steele asked if more could be said about the collaboration/pilot project with UT Southwestern listed on Dr. Kupersmith's slide, as well as the brain/tissue and gene bank proposals. Dr. Kupersmith stated that they were just being to work out the details for the initiative with UT Southwestern., and really couldn't talk about it any further detail because it was so preliminary.

Chairman Binns commented that he was pleased to see VA ORD proceeding with the Gulf War brain/tissue and gene bank projects. Mr. Robinson reminded the Committee and VA officials about a veteran who had offered to donate his brain to this type of organ bank. He stated that the veteran was not doing well, and was not expected to live much longer. He stated that the veteran and his family were still interested in donating his brain. With regards to the gene bank initiative, Mr. Robinson noted that the VA is holding serum samples, which were taken from 600 veterans before and after deployment to the Gulf.

Dr. Timothy O'Leary spoke to the Committee about the tissue bank project. He stated that it would take some time to establish because of its complicated nature. He stated that the VA currently had limited mechanisms with which to respond to offers such as the veteran mentioned by Mr. Robinson.

Ms. Nichols thanked VA ORD and the Committee for following up on the brain bank. She stated that the idea had been long discussed in the Gulf War community, and many would be happy to see it put into place.

Dr. O'Leary commented that VA ORD anticipated the tissue bank would include a variety of tissues from a variety of different individuals, including those who died with chronic multisymptom illnesses. He noted that specimens from controls would also be collected. He stated that they were still in the design process, but anticipated that the bank would be up and running within six months. The initiative would be run out of the VA's cooperative studies program, using a biorepository trust model developed by the Massachusetts Veterans Epidemiology Research and Information Center (MAVERIC). The physical tissue repository would likely be in Tucson, AZ, with management of consent running out of a coordinating center in Palo Alto, CA. It will be designed to operate nationwide.

Dr. O'Leary stated that they were also looking at establishing a DNA bank. They were considering the feasibility of sampling from Phase III of Dr. Kang's study, along with broader sampling strategies, in the development of this repository. He stated that the idea was to develop a way to understand why individuals exposed to a toxic insult might vary with respect to the effects of that toxic insult. He noted that there were a variety of nucleic acid alterations that were predictive of changes in metabolic pathways. Ultimately, they would be looking to determine what genetic factors are important in physiological responses to toxic agents. However, genetics would not be the whole story. He stated the time frame goal was the same, i.e., within the next six months.

Dr. Steele commented that these initiatives were wonderful. She asked whether investigators who had worked on previous efforts to create a VA brain bank were involved in this endeavor. Dr. O'Leary noted that MAVERIC had developed a multicenter tissue banking proposal, however, it was directed solely at brain tissue collection. He stated that VA had other tissue banking efforts underway, but these models weren't specifically applicable to this particular community. This was because the specimens were collected from much older veterans who were not as widely dispersed. In order to obtain an adequate number of specimens for research in a finite time, they will need to cast the net more broadly.

Dr. Steele asked if the DNA and brain tissue banks would be physically located at a centralized facility. Dr. O'Leary stated that the repositories could be separate. He noted that VA was a health care system in which a virtual bank, with multiple storage locations, was possible. He acknowledged that virtual banking was more likely with DNA than tissue, and might have problems when it comes to information technology. Dr. Golomb asked if other tissues were being considered for collection, as there were Gulf War veteran pathologies that went beyond the brain. Dr. O'Leary stated that they were considering this, and it would depend on the type of consent of the veteran. He noted that some states allowed pre-mortem consent while others did not, so obtaining the family's cooperation was very important.

Dr. O'Callaghan asked if they were considering sampling fresh brain specimens. Dr. O'Leary stated they were, and that the idea was to obtain fresh specimens in a number of different ways. Some samples would be considered useful for anatomical purposes, while others would be intended for biochemical and genetic analyses. Dr. O'Callaghan asked if this would be part of the sampling protocol under development. Dr. O'Leary said it would be.

Dr. Joe Francis, Deputy CRADO, noted a recent article in the *New England Journal of Medicine* about health information altruists and the ethical dilemmas of providing genomic information. He stated that researchers must rely on individuals being altruistic in providing this very personal information about their bodies. He couldn't identify a more altruistic group than veterans in this respect. He commented it was difficult to coordinate a national program such as genomics or brain banking. He stated that, given these difficulties, progress in this area was considered rapid. He stated they were developing a central institutional review board (IRB) process to overcome these hurdles.

Dr. Steele asked if there was a DNA banking component to the VA's ALS registry. Dr. O'Leary stated that there was, but that it was not intended to facilitate identification of potential donors outside those with ALS diagnoses and so was not specifically a resource for Gulf War illness research. He stated that the ALS registry also included the broader veteran community, i.e., it was not limited to the Gulf War. Dr. Kupersmith commented that the approach was to first ask what research questions needed to be answered, and then determine the manner in which the specimens should be collected.

Chairman Binns asked Dr. O'Leary if he would give a brief description of a DNA bank. Dr. O'Leary stated that the process starts with informed consent. The next step involved donations, which can be obtained in a number of different ways. One method can be as simple as obtaining cells from one's cheek. However, not much DNA can be collected via this method, so it was a limited collection technique and wasn't ideal. The second approach would be to take a blood sample, separate the white blood cells, and extract the DNA using various chemical approaches. Both of these approaches can be amplified using available technology. The third approach, which is the most interesting and most expensive, is to take the blood cells, infect them with an Epstein-Barr virus to make them immortal, and propagate them as a cell line. He stated that it was likely they would be looking at all of these methods. In some populations, it may be appropriate to establish cell lines. In other instances, some veterans may feel comfortable giving a donation in one form, but not another. He noted that this was a great gift from the veteran to the research community and nation as a whole.

Dr. Golomb asked if this project would focus on the nuclear genome. Dr. O'Leary noted that mitochondrial DNA would be present in the samples but the problem with mitochondrial DNA was that it can be different depending on sample site. He noted that mitochondrial DNA replicated at a different rate in lymphocytes compared to muscle cells. However, doing muscle biopsies was a separate issue. His perspective was not to do muscle biopsies at this time, but that this type of sampling could be part of a specific investigation. Dr. Golomb noted that mitochondrial DNA mutates 1000 time faster than nuclear DNA. She also noted that several conditions in which the Committee is interested, e.g., ALS and Parkinson's disease, have a known association with mitochondrial pathology. Dr. O'Leary stated that he anticipated the tissue collection would be relatively slow in comparison to the DNA collection.

Mr. Robinson asked if there was any way to inform the family of the dying veteran that VA was committed to moving forward on this issue, and that their input was valuable in getting this movement underway. Dr. O'Leary stated that VA absolutely was committed to doing this program, and encouraged Mr. Robinson to inform the family about it.

Dr. Meggs commented that any family could request an autopsy and the collection of certain samples. The sample collection may or may not meet the protocol standards down the line, but many preservatives and collection techniques are standard. Many people have done this in the hope that the specimen would be useful at a later time. Dr. Steele noted that the Armed Forces Institute of Pathology (AFIP) would accept tissue samples from Gulf War veterans for its repository. The only issue is obtaining an autopsy conducted at VA, which in turn raises the issue about the cost and who pays for it.

On behalf of the Committee, Chairman Binns thanked Dr. O'Leary for ORD's response to this issue.

Gulf War Update

William J. Goldberg, PhD
Gulf War Research Portfolio Manager, VA Office of Research and Development

Dr. Goldberg gave an update on: (1) the newly-established criteria used to determine whether a particular study would be included in VA's ORD Gulf War research portfolio; (2) VA's progress with respect to addressing the Committee's 2004 report recommendations; and (3) the status of the Annual Report to Congress on Federally Sponsored Research on Gulf War Veterans' Illnesses. (See Appendix A – Presentation 9.)

During the discussion of the Gulf War research portfolio, Dr. Golomb expressed concern about including studies that focused on stress, referring to several specific projects listed as part of the portfolio such as "Effects of Stress on Memory: Brain Circuits, Mechanisms and Therapeutics." Dr. Goldberg stated that alterations in processes associated with the HPA axis might be a factor in veterans' illnesses. He said it wasn't necessarily "the" factor or the cause, but that it should not be ignored. Dr. Golomb noted that the Committee had expressly recommended that stress studies no longer be funded with Gulf War research funds. She agreed that these were important areas of research, but that they were not recommended as the focus of studies funded as Gulf War illness research.

Dr. Goldberg stated that they were attempting to construct a very broad based portfolio of research on Gulf War veterans' illnesses. He understood that the Committee had its focus, and said that the Committee's advice was taken very seriously. However, VA also had a mandate to study, in their best scientific judgment, all aspects of illnesses affecting Gulf War veterans. Dr. Golomb pointed out that the purpose of having special Gulf War research money was that Gulf War veterans were experiencing conditions that are different than other veteran groups. She questioned Dr. Goldberg as to whether Gulf

War veterans had higher rates of PTSD than veterans from other wars. Dr. Goldberg stated that they were not looking at the HPA axis in terms of it causing PTSD. This was not the reason for including these studies in the Gulf War portfolio. These studies were included in case Gulf War veterans had altered immune or HPA function, which caused them to respond to their environments differently.

Mr. Graves acknowledged that "stressors" are a factor. Dr. Goldberg agreed, and stated that is why this type of research was included in the portfolio. Dr. Golomb stated that the Committee did not dispute that stress was an important area of study for veterans. However, it was not an important area of study for the special, and different, categories of illnesses experienced by 1990-1991 Gulf War veterans. She stated that the HPA axis alteration study related to PTSD.

Dr. Meggs commented that it would be reasonable to study differences in neurohormonal regulation among Gulf War veterans, and determine if there were biochemical markers for these alterations. Dr. Goldberg stated that this is why these studies were included in the portfolio. Dr. Golomb stated that it wasn't that she didn't think this was important research or that it would be lead to a dead end. She expressed her opinion that it just wasn't specific to 1990-1991 Gulf War veterans. Dr. Goldberg stated that the listed studies were specially looking at ill Gulf War veterans to see if they showed evidence of unique changes. Dr. Meggs stated that it appeared the researcher was going to look at biochemical measurements of neuroendocrine function in ill Gulf War veterans versus a control group. Dr. Golomb asked if both study groups were PTSD groups. Dr. Steele stated they were talking apples and oranges. She agreed with Dr. Golomb's general point, but pointed out that the first study listed ("Evaluation of Stress Response Systems in Gulf War Veterans with CMI") addressed biological stress responses in chronic multisymptom illness. The PTSD study being discussed was a separate project.

Dr. Goldberg stated that there was information of value to be gained from the disputed study. Dr. Golomb did not disagree that there was information of value, which would be especially important for the troops currently deployed in Iraq. However, it isn't the area of specific interest for the distinct health problems associated with 1990-1991 Gulf War service. Dr. Steele pointed out that the case control groups were PTSD vs. no PTSD, as opposed to Gulf War vs. non-Gulf War veterans. Dr. Goldberg stated that they would be working with the investigator to perhaps modify the protocol slightly to ensure additional data were collected that would be applicable.

Chairman Binns stated that he agreed with Dr. Golomb, but noted that the PTSD study began in 2003. He noted that VA's commitment to not fund stress-based research began in FY2005. Dr. Golomb thanked Chairman Binns for noting this point. Dr. O'Leary stated that, from his scientific perspective, the important thing was to figure out what was going on. He noted that stress had many different forms, including physiological forms. He stated these were issues that needed to be thought about and investigated. He recognized that there may be some difference in opinion between members of the Committee and VA ORD. However, he also thought it was important to recognize that the primary objective remains the same. These studies were not a major focus of the program, but weren't discounted. He stated, however, that he was aware of Dr. Golomb's concerns about inclusion of these studies in the portfolio.

Mr. Graves stated that he agreed with Dr. Golomb and the spirit of what she was trying to accomplish. He pointed out that it had been 15 years since the Gulf War, and for 12 or 13 of those years, stress was the primary research focus. He said that there had been ample opportunity and funding to study stress in the past but that since there wasn't a lot of money available for Gulf War research, the Committee just wanted to make sure it was now being used in a more targeted and strategic way. He stated that when he sees these types of studies sprinkled through the portfolio, he becomes concerned.

Chairman Binns noted that several of the studies which concerned the Committee were funded prior to VA's commitment to not fund new Gulf War stress research. He stated that the question was whether there were stressed-based studies funded in FY2005.

Mr. Graves noted that, when the Committee visited the East Orange, NJ, War-related Illness and Injury Study Center (WRIISC) in June 2004, he had been disappointed by some of their proposed studies and was further disappointed when these studies were funded. He stated that if nothing could be done about the previously funded studies, at least Drs. Goldberg and O'Leary had heard the Committee's concerns about future funding. Dr. O'Leary acknowledged this concern, but wished to make a strong distinction between PTSD and physiological stress associated with deployment. Dr. Golomb stated that the Committee was very familiar with that distinction.

Dr. Steele stated that there were a number of individual projects included among studies that had been newly-funded in FY2005 that the Committee might not consider to be ideal. The Committee's meeting binders included tables that summarized the focus of these studies, distinguishing between studies that addressed Gulf War illnesses and effects of exposures, psychological stress, ALS in the general population, and ALS in relation to Gulf War service. Overall, FY2005 Gulf War research funding totals included 17% for studies focused on psychological stress and psychiatric illness. She compared this with the FY2003 portfolio, for which over 50% of funding was for studies on psychological stress and psychiatric illness. Overall, she noted that the proportion of stress-focused studies had gone way down in this period. Dr. Goldberg agreed that this was the trend in the last RFA funding cycle.

Dr. Goldberg stated that part of this was due to a more refined RFA for 2005 proposals. The 2005 RFA provided much better direction and a list of suggested topic areas. He stated that having the list of topic areas helped the researchers refine their proposals to make sure that they were responsive. He hoped to get the next RFA out in January or February 2006 and requested input from the Committee on priority topic areas. The more direction VA ORD could give to the field researchers, the more likely they were to get the desired research projects. Chairman Binns welcomed Dr. Goldberg's invitation to help develop much more refined descriptions of the studies should be conducted. He noted for the Committee that the FY2005 RFA boldly stated that VA ORD was not funding studies based on the notion that stress is the underlying cause of Gulf War illnesses. Dr. Steele commented that this statement had worked, resulting in fewer such proposals.

Dr. Goldberg stated that, after finishing two funding cycles with a substantial number of approved projects, VA researchers were getting the point that this was a serious area of research. He noted that most of the proposals were coming from the Biomedical and Clinical Sciences services, which had a one-funded-proposal-per-investigator rule. He stated that an exception had been granted with regards to Gulf War proposals, allowing an investigator to apply for two grants. He believed there was a more positive perception among VA researchers that this was an area of research worth engaging in.

Besides recommendations as to what should be included in the RFA, Dr. Goldberg stated that he also would welcome particular recommendations with regards to proposals that shouldn't be considered. Mr. Graves expressed his displeasure with the telemedicine study listed in the portfolio. Dr. Goldberg stated that Dr. Kupersmith and he had spent considerable time looking at the various proposals, trying to determine if they provided information that would aid in understanding what was happening in Gulf War veterans. He noted that there were several studies included in last year's portfolio list that weren't included this year.

Dr. Steele pointed out to the Committee that information summarizing all projects included in the current Gulf War research portfolio was included in their binders. She noted that although the proportion of

newly-funded studies dedicated to psychiatric illness and stress studies had decreased, the portfolio still contained studies that the Committee would not consider to be Gulf War-specific. She noted that about one third of the portfolio monies were allocated to general ALS research not specific to the Gulf War. Dr. Goldberg commented that he wasn't sure he could separate a Gulf War veteran with ALS from anyone else with ALS. He stated that ALS had been service-connected for Gulf War veterans. He also guaranteed the Committee that all of VA's new ALS research was not included in this portfolio. He stated that there were a number of ALS studies that he felt were too far afield with regards to Gulf War veterans. Mr. Smithson clarified that ALS had not been presumptively service connected for Gulf War veterans. Dr. Goldberg agreed it wasn't presumptively service connected, but the ability to get a service connection had been streamlined. Mr. Smithson stated that there was a difference, and that he wanted to make it clear that VA could stop service connecting tomorrow without a presumption in place.

Chairman Binns stated that there were two issues on the table now: (1) What was funded under the FY2005 Gulf War RFA?; and (2) What is included under the Gulf War research portfolio, which covers multiple studies funded over the years and not necessarily studies that had been funded through the Gulf War RFAs? This leads to two separate questions: (1) Does the Committee agree with what VA is doing under the Gulf War RFA?; and (2) Does the Committee agree with their characterization of VA's overall Gulf War portfolio?

Chairman Binns asked if there was any discussion on the newly-funded projects. Mr. Graves suggested that future studies not focus on temperature extremes. He stated that heat wasn't an issue between October 1990 and April 1991. He stated that they fought in the rain. He acknowledged this would probably be a factor for the currently deployed troops, but not those in 1990-1991. Mr. Robinson noted that there were issues with high heat during the early build-up to the war (August to mid-October 1990), especially with soldiers wearing mop suits, but agreed that high heat was much more important with the current deployment. Dr. O'Callaghan commented that, in terms of neurotoxic effects, physiological and environmental factors such as temperature are increasingly recognized to play an important role. Dr. Golomb agreed.

Dr. Haley asked for clarification and justification for inclusion of certain studies in the Gulf War portfolio. The first study dealt with coagulopathy. Dr. Golomb stated that this was linked with CFS and fibromyalgia conditions. It involves reduced delivery of blood and oxygen to tissues. She believed that there was one published article that reported such abnormalities in Gulf War veterans. The second study involved experimental lung injury in response to heat exposure. Dr. Haley acknowledged there were issues involving oil well fires, but lung conditions weren't really evidenced in Gulf War veterans. Dr. Steele stated that Committee staff had classified this study as having only remote relevance to Gulf War veterans and that this study had been funded under the most recent RFA. Dr. Haley stated that this appeared to be an issue of the proposal review group not really understanding the focus of the RFA. Dr. Golomb asked if it was possible for the Committee to review the approvals. Dr. Goldberg stated that this wasn't possible. Dr. Golomb indicated that the point wouldn't to be to pick or choose the studies, but to help identify proposals that clearly weren't germane to Gulf War veterans' specific health issues. Dr. Goldberg stated that regardless of the system used, there would always be one project that the Committee and ORD would disagree on. He wasn't sure if there was a way to avoid this happening.

Mr. Robinson asked if Dr. Goldberg's comments regarding the Committee's review of proposed projects were based on his own opinion or a legal definition of the Committee's charge. Dr. Goldberg stated it was the legal definition of the Committee's charge. He stated that the Committee is charged with providing advice and recommendations to the Secretary. It was not to be involved in the peer review process. He stated that when Dr. Steele was participating in the review meetings, she was doing so as an

epidemiologist from Kansas State University. She was not there representing the Committee in her role as Scientific Director.

Chairman Binns commented that there was a case to be made on both sides as to whether the Committee should review the proposals. Agreeing to disagree on this point, he didn't believe there would be any disagreement that VA's review process for Gulf War proposals had been materially improved by having a member of the Committee with specific scientific expertise on Gulf War illnesses sit on the review panel. He noted that many of the less desirable studies funded in 2004 came out of the review panel without such an individual. He suggested that including more members from the Committee, in their independent scientific capacities, on these review panels might be a good thing. This was not because of a requirement that they be on the review panel, but because their contribution could be beneficial. Dr. Goldberg stated that the main criterion for serving on a merit review panel was having the appropriate scientific expertise.

Dr. O'Callaghan commented that he had previously served on a Gulf War merit review panel. He remembered being struck by the fact that it was unclear how the proposals related to the RFA. When he looked at the RFA, he was unclear as to the intended scope of the proposals. He had the impression that there had been no triage of the studies before they were reviewed by the panel. Dr. Goldberg stated that there was an agreement with VA field researchers that ORD would not use an abstract or short description to eliminate a project before a merit review committee had a chance to see the actual study being proposed. Dr. O'Callaghan commented then that it seemed the Committee needed to provide more specific RFA development advice.

Dr. Goldberg asked Dr. Steele for her thoughts on the manner in which the relevance issue was handled at the most recent 2005 merit review panel. Dr. Steele stated that relevance to the RFA had been a major focus for the panel on which she served. Dr. Goldberg stated that there had been extensive discussion of relevance, on many levels, by both panels in 2005. He indicated that the review process had been significantly altered from previous years, with which Mr. Robinson agreed.

Dr. Steele stated that the Committee had been provided with a separate summary of the twelve projects recently funded under the FY2005 RFA that was being discussed. She noted that there were no stress studies in this group, and 85% were Gulf War specific or related to effects of Gulf War exposures. She stated that the proportions were a remarkable departure from funding for studies resulting from previous announcements.

Dr. Haley asked Dr. Goldberg about the proposed projects that had not been approved for funding. He expressed concern that these projects may be much more relevant than those approved. Dr. Goldberg stated that the projects turned down were so scientifically flawed that they weren't salvageable. The merit review panel was given clear instruction on scoring, with an absolute cut-off score of 22. He explained that the scale range was 10 to 50, with 10 being the best and 50 being the worst. Scores of 22 and below are in good enough shape to proceed but may have some flaws. Scores above 22 were considered so scientifically flawed that it would be untenable to proceed with them at that time. He stated that the review panels provide the researchers with an explanation of what was wrong with the proposal, whether it was technical or design flaws, and that it could be revised and resubmitted. VA ORD has told the field that there is going to be another RFA, so the researchers are aware that there will be a chance to redesign and resubmit these projects. He stressed that no proposal was turned down because somebody didn't recognize its value. The merit review panels were instructed to evaluate quality of the projects, relevance to Gulf War veterans' illnesses, and relevance to the RFA itself. Dr. Steele commented that there weren't any borderline cases reviewed by the panel she sat on, and that there were scientific issues with the rejected proposals. She was encouraged to see a higher proportion of Gulf War-specific studies

funded under the last RFA. However, the goal now should not just be to fund studies that are relevant, but to fund studies that address key research questions that have a high priority for understanding Gulf War illnesses. Chairman Binns added that the vehicle for this was the RFA; and the RFA needs to list the most relevant topics.

Mr. Robinson commented that he was appreciative of steps taken by VA ORD to address the veterans' concerns. He indicated that he could articulate this now to the veteran community and let them know that their concerns were being heard, even though this is a scientific endeavor. Dr. Goldberg stated that when the criteria were distributed for comment in other ORD sections, a Gulf War veteran commented "so you are finally going to study my issues." He hoped that the Committee sensed that VA ORD is listening to the Committee's concerns, and that they are trying to focus on the illnesses affecting Gulf War veterans.

Mr. Graves inquired about standards for administrative overhead costs for research projects. Dr. Goldberg stated that the 12.5% allocated for this by ORD was very low.

Chairman Binns commented that the Committee had been fighting "this war", if you will, for four years, and that this was an enormous step forward in just a few months. He stated that current ORD officials had done everything they could do, short of putting a few more people on the merit review panels, given the point at which they came into the process. He noted that there was nothing grossly irrelevant that had been funded under the last RFA and 85% of the studies were relevant. He noted that Dr. Goldberg had not crafted that RFA, but would craft the next RFA to be more specific. He noted that the last RFA wasn't highly publicized, so hopefully the number of proposals received under the new RFA would be greater. Dr. Goldberg stated that they had tried to do a better job publicizing the last RFA when it was announced. The interesting thing was that the number of intents to submit and actual number of proposals was similar between the FY2004 and FY2005 submissions. He suspected that after two cycles of funding, there was a better perception of the chance of funding, and that they would see an increase in the number of submitted proposals.

Chairman Binns added that the Committee was disappointed to see that only $1.7 million had been spent on these new studies, as opposed to up to $15 million, which was what Secretary Principi had announced. Dr. Goldberg stated that whether this announcement applied only to "new research" was controversial as was the issue of "up to" versus "$15 million" in any particular year. Chairman Binns offered to show Dr. Goldberg a copy of Secretary Principi's public comments. Dr. Goldberg stated that ORD had made a firm commitment to spend $15 million on Gulf War research in FY2006, and that some of this money was earmarked for the tissue/DNA banks and the Gulf War treatment research center. He explained that this accounted for the difference between the $11.3 million listed on the portfolio summary sheet and the promised $15 million.

Chairman Binns stated he didn't want to belabor the point, but Secretary Principi had committed up to $15 million of new research beginning in FY2005. Going forward, he said that the Committee would hope that the percentage of new research would increase and that these studies would be relevant. He noted that the main disagreement at this point was how ORD was categorizing previous funding decisions in order to give the appearance of a higher dollar commitment to Gulf War illness research. He reiterated that there was agreement with the steps taken with respect to new research, and applauded the direction being taken by Dr. Goldberg.

Dr. O'Leary noted the Committee's perspective on this, but in terms of any clarification, ORD would have to defer to the Secretary. He said that VA shared the commitment of doing high quality research in this area and that they are trying hard to get there. VA has to meet a number of different imperatives and

consider advice from a number of different sources, such as the U.S. Government Accountability Office (GAO). The end goal for both VA and the Committee is to not fail these veterans.

Chairman Binns stated that his only suggestion was that the current VA ORD officials not feel obliged to defend the past. Dr. Goldberg agreed that there were things done in the past that were not appropriate. He stated that ORD had carefully evaluated what was currently included in the Gulf War portfolio and that it was, in their overall opinion, their best sense of a balanced and complete portfolio, looking at many of the illnesses and symptoms experienced by ill Gulf War veterans and possibilities for new therapies. He stated that the ultimate purpose of this effort was not to study Gulf War veterans' illnesses, but to find therapies to provide relief to these veterans. Dr. Golomb stated that the Committee agreed, and this is why the Committee was so intent on making sure that the focus was on understanding mechanisms, which should help ultimately to develop treatments.

The meeting adjourned at 10:11 a.m. for a break.

The meeting reconvened at 10:28 a.m.

Regarding the need for epidemiologic studies to determine the prevalence of serious neurological conditions in Gulf War veterans, Dr. Goldberg stated that no proposals had been received with regards to Parkinson's disease. There had been one proposal that would have looked at multiple sclerosis (MS), but it had been scientifically flawed. Dr. Haley asked if any data had been published by the Duke researchers with regard to the National ALS registry. Dr. Steele stated that a methodology paper had been published in 2004, and suggested getting an update on their research at a future Committee meeting. Dr. Haley agreed.

Mr. Graves commented that Committee criticisms concerning VA's research program were not directed at Dr. Goldberg personally. Dr. Goldberg stated that he hadn't taken it that way and understood that the concerns raised by the Committee were honest scientific and personal concerns about the direction of the Gulf War research program. He added that there didn't need to be universal agreement on every topic, but the more information that could be given to the field, the better the proposals would be. He looked forward to receiving suggestions from the Committee on research priorities for the next RFA.

Dr. O'Leary commented that although serious attention would be given to comments from individual Committee members there was more value and weight given to formal recommendations provided by the Committee acting in concert. Dr. Steele noted that the Committee had already assembled and provided lists of priority research topics to ORD in connection with previous RFAs. She thought that recommendations for the next RFA would include many of those, with some additional recommendations based on new information and recent discussions.

Dr. Goldberg proceeded with his presentation, providing the Committee with an update on the Deployment Health Working Group and its Annual Report to Congress on Federally Sponsored Research on Gulf War Veterans' Illnesses. He outlined the 21 Gulf War research priority questions established by the working group in previous years, and described how studies funded by the three agencies were included in the federal Gulf War research database.

Mr. Robinson asked if VBA/VHA data or epidemiology study data were used to evaluate the Annual Report's relevancy and priorities. Dr. Goldberg stated that epidemiology studies were the primary source of information. Mr. Robinson suggested also using the ICD-9 codes of Gulf War veterans within the VA system to determine what health problems were prevalent. Dr. O'Leary expressed two concerns with using that approach: (1) possible epidemiological bias due to differences in the populations enrolled in the

VA system; and (2) VA isn't the only agency involved in the process. Identification of priorities and review of the Annual Report were done by all three agencies (VA, DoD and HHS), which have different cultures.

Dr. Haley noted that the Committee had heard previous presentations about attempts to perform analyses using VHA databases. Dr. Steele commented that the Annual Report, in its current form, was not about how many people have a particular condition, but described the types of studies and levels of funding allocated for Gulf War research. But she agreed with Mr. Robinsons' general point that the highest research priority should be given to studies of conditions that were more common among Gulf War veterans than nondeployed veterans. Dr. Golomb added that Gulf War research should also focus on conditions and symptoms that don't currently have treatments. She noted that asthma may be elevated in this population, but there were already treatments available for this condition. She agreed that there was a need to fully describe the elevated conditions in Gulf War veterans. She noted that she, personally, probably wouldn't put pulmonary symptoms or diagnoses on the high priority list.

Mr. Smithson noted that VBA data don't provide a breakdown of conditions associated with claims that were denied, that is, information is only provided on conditions for which service-connection had been granted. Dr. Steele added that although this detailed information was not in the Gulf War Veterans Information System (GWVIS) Report, information could be obtained on the number of claims made by Gulf War veterans for any specific condition, including the number of claims approved, denied or still pending. Mr. Robinson commented that VA was tracking the current war's veterans by ICD-9 code. This presented a picture of the problems being seen in these veterans. He hadn't seen a similar breakdown for Gulf War veterans, despite there being over 365,000 individuals in the VA system.

Dr. Goldberg described the categories used to group the federal Gulf War research studies. Dr. Golomb asked whether "exposure studies" referred to studies that evaluate the impact of an exposure or determine the level of exposure. Dr. Goldberg stated that the original questions had been focused on epidemiology, e.g., "What is the prevalence of X?". However, the studies being assigned now to these categories may no longer be epidemiology studies but studies related to mechanisms and effects of exposures. He noted that the questions currently included on the list would be reassessed and that after this process, it was likely that even existing questions that remain on the list would need to be rephrased.

Chairman Binns asked if Dr. Goldberg would be the individual responsible for drafting the Annual Report. Dr. Goldberg indicated that he would have primary responsibility, but reiterated that the report was a multi-agency project.

Dr. Golomb suggested expanding Question 17 beyond the effects of short-term low-level exposure to PB, DEET, or permethrin, because there were other pesticides to which the troops were exposed. Dr. Goldberg agreed. Dr. Golomb noted that several of the new research proposals addressed the exposure combination of PB, DEET and permethrin. Dr. Goldberg stated that this may have become "the" combination, but the RFA could purposefully expand the combinations recommended for study.

Dr. Goldberg commented that the VA Gulf War research portfolio had included very few projects related to reproductive health and that this area was not being addressed by any agency's Gulf War research portfolio. Dr. Haley noted that early epidemiologic studies hadn't revealed much in this area, but more recent and better-designed studies had shown positive associations between birth outcomes and Gulf War service. Dr. Steele noted Dr. Araneta's previous comments to the Committee about there being no funding available for this type of research. Dr. Haley stated that the research questions in this area should be reframed based on current epidemiologic findings in order to determine where the critical issues are.

Dr. Goldberg stated there was a fair amount of work that needed to be done on the Annual Report, in addition to reviewing and restructuring the identified research priorities.

Dr. Goldberg described how data were encoded in the federal database that encompassed VA, DoD, and HHS information on Gulf War research. He stated it was more of a repository than a functional database. They currently are in the process of revamping it, and have sent the revised shell to DoD and HHS so that they can enter their data. VA will be the agency organizing all of the data. The next step in the process would be to analyze the data, and begin writing the Annual Report.

Dr. Steele commented that, in previous years, the category "Brain and Nervous System Function" always included both psychiatric and neurological studies, thus giving the impression that there were more neurological studies. She suggested that these studies no longer be combined in future reports. Dr. Goldberg stated that he would bring that suggestion to the Research Working Group subcommittee.

Dr. Meggs commented that Gulf War veterans were homogenized with the other veteran populations at VA clinics. He suggested having designated primary care physicians at each clinic that saw all the patients in the Gulf War cohort. He stated that this would provide a tremendous resource of information. He noted that these physicians would become more sophisticated with the diagnostic coding, but might also begin seeing patterns. Dr. Goldberg stated that the Gulf War database wasn't a patient record database, but rather a database of research studies funded by the federal government. He stated that neither the Research Working Group subcommittee nor ORD had the standing to advise VA clinical services how to practice medicine. Dr. Meggs noted that this might be a good thing for the Committee to recommend to the Secretary. Ms. Nichols asked whether this might fall under clinical research. Chairman Binns stated that it wasn't "research", but the Committee could comment on it. Dr. Goldberg stressed that the Annual Report was a report to Congress explaining how federal research monies had been spent in a particular year, along with accomplishments and future directions.

Ms. Knox expressed concern about removing psychiatric conditions from the report, because new science was showing that these were brain disorders with a biological basis. She was afraid something might be missed. Dr. Golomb stated that she understood Dr. Steele's suggestion was to categorize psychiatric and neurological research separately, not to remove psychiatric research completely. Separation of these categories would help to quickly determine how much money is going to each category.

Dr. Steele inquired about the status of the Deployment Health Working Group and its Research Working Group subcommittee. Dr. Goldberg stated that the Deployment Health Working Group met on a monthly basis. He identified several members including Drs. Mark Brown, Susan Mather, Kelly Brix, and Michael Kilpatrick. Dr. Goldberg noted that Dr. O'Donnell, a UK Ministry of Defence (MoD) liaison, and he himself attend many of the meetings as well. Dr. Goldberg stated that the Research Working Group subcommittee did not meet as often, but this would change when it was time to draft the Annual Report. He stated that the focus of the Deployment Health Working Group right now was on seamless transition and Operation Iraqi Freedom (OIF) and Operation Enduring Freedom (OEF).

Chairman Binns asked if the Deployment Health Working Group meetings were open to the public. Dr. Goldberg stated that they were not because this committee was not subject to FACA. Mr. Robinson noted that he was not aware of any publication of their recommendations.

Dr. Steele asked Dr. Goldberg to discuss the Gulf War treatment center RFA. He stated that because the RFA was in concurrence, the specific document couldn't be handed out and discussed page by page. However, he could talk about several aspects of the treatment center that were points of concern in earlier discussions. The first issue was the level of protected time for the center director. This had been set at a

minimum of 3/8ths time, and required a written commitment by both the medical center director and VISN director. He said there would also be the option of having a center scientific director, creating two high-level leadership positions. This mechanism should give strong leadership and keep the research enterprise going in the direction needed. Discussion followed about difficulties in obtaining protected research time for VA clinicians and the separation of clinical and research appropriations.

Chairman Binns asked Dr. Goldberg to provide the "big picture" of what the treatment research centers would be doing. Dr. Goldberg discussed various aspects of the treatment center concept and indicated that funding would be made available for up to 3 centers. One of the purposes of the centers would be to collect and analyze data on therapeutic interventions currently being used to treat Gulf War veterans in various locations. This would be a "clearinghouse function" of the treatment centers. He listed other aspects, including looking at treatments for other multisymptom illnesses, improving case definitions, determining proper measurement end points, and evaluating biomarkers and other approaches for monitoring effectiveness of treatments. He noted that a goal of these centers is to conduct pilot research on clinical interventions that could be used to lay the groundwork for larger multi- or single site clinical trials.

Mr. Robinson asked if Dr. Goldberg knew where these treatment centers would be located. Dr. Goldberg stated that he didn't, because they hadn't started receiving proposals yet. He would like to see them scattered, but this would depend on where the proposals come from. He suspected that proposals will be received from around the country. Mr. Smithson asked if there would be an effort to avoid concentrating them in one geographic location.

Chairman Binns clarified that these would not be treatment centers where veterans would go to seek special treatment for Gulf War illness. The purpose of these centers would be to develop information on potentially beneficial treatments and then do pilot studies. He stated that Dr. Steele had spent a considerable amount of time explaining what the Committee was recommending. This is something that is not commonly done in academia or government sectors. He was very pleased that the RFA reflects the concepts that the Committee had emphasized. Dr. Steele noted again that this would not be a center where veterans would be referred for treatment, unless they were involved in a pilot study. She stated that while dispersal around the country would be great, the main focus will be data collection.

Dr. O'Leary stated that that the treatment center research review panel would be looking at the following, in this order: (1) scientific merit, including program relevancy; (2) overlap and avoiding inappropriate overlap with other centers; and (3) geographic dispersion. He didn't think geographic location would be a major concern. He stated that the aim was to develop research ideas. Dr. Goldberg added that the geographic distribution tended to work itself out with the diversity of submitted proposals. Dr. Golomb noted that that the two WRIISCs were located close together (East Orange, NJ, and Washington, DC). Mr. Smithson stated that he had spoken with Dr. Mark Brown numerous times about the problems with accessibility to the WRIISCs.

Dr. Steele commented that it wasn't just the Committee saying this over the past few years, but that veterans and many others had been saying for many years that treatments for these conditions were badly needed and should have high priority. She thought that soliciting proposals for the treatment research centers was a huge step forward and was pleased to see it being done. Ms. Knox asked what treatments the centers would be assessing. Dr. Steele stated that these centers would be "casting the net" and determining what people are trying/using and what has been effective. Dr. Goldberg commented that this was the advantage of having three centers. It allowed for a wider variety of focus areas, while encouraging collaboration and cooperation between the study centers. Dr. Haley commented that the end

goal of these treatment research centers was to identify promising treatment that could be put into a collaborative studies program or clinical trial.

Dr. Goldberg stated that VA's Clinical Science Research and Development service conducted single-site clinical trials and that the Cooperative Studies program within that service conducted multi-site trials. This provided the vehicle by which the treatment research centers' findings could be investigated further. The treatment research center will provide the preliminary data for these larger clinical trials. Ms. Knox inquired about the VA's sleep study centers. Dr. Goldberg stated that the VA had two premier clinics, one located in San Diego and the other in Boston. He stated that neither center is currently doing Gulf War research but he had spoken with the group in San Diego about this possibility.

RAC Business

Lea Steele, PhD
Scientific Director, Research Advisory Committee on Gulf War Veterans' Illnesses

Dr. Steele gave an overview of Committee business and anticipated activities for the coming year, including the 2006 Committee report and possible areas of focus for 2006 meetings. (See Appendix A – Presentation 10.)

With respect to the 2006 report, Dr. Steele asked if the Committee wished to address topics in addition to those outlined. Dr. Meggs noted that the Committee had devoted a good part of a meeting to other complex multisymptom illnesses and how these illnesses may relate to Gulf War illnesses and believed that the report should address this topic. Dr. Steele agreed, and thought that the report should include information about the prevalence of these illnesses in Gulf War veterans and what areas of research on these conditions may be applicable to Gulf War veterans. Dr. Meggs agreed.

Dr. O'Callaghan suggested that the Committee address end-organ inflammatory responses underlying these multisymptom illnesses. He would like to see this area fleshed out. Dr. Steele agreed, and stated that this would a topic that the Committee would be focusing on in upcoming meetings. She stated that findings about this topic would not be included in the 2006 report since the information had not yet been reviewed by the Committee, but the next phase of the Committee work would address it. Dr. O'Callaghan noted that many of the symptoms affecting Gulf War veterans, like pain, have inflammatory components. This is an emerging theme in contemporary neuroscience.

With respect to future directions, Mr. Robinson commented that the Committee had a responsibility to help educate VA clinicians and there was a need to improve the Veterans Health Initiative (VHI) training series for Gulf War illnesses. He stated that the VHI guidelines were outdated and needed to be updated. Chairman Binns stated that perhaps the report could make a recommendation that the Committee's findings be communicated to VA clinicians and elaborate on how this might be done.

Ms. Knox questioned the likelihood of clinicians reading an entire bound booklet, but suggested summarizing key presentations and having researchers provide a continuing medical education course on the topics. Dr. Golomb noted that clinicians were poorly trained by the current VHI series and it might be advisable to require everyone to undergo this training again. Mr. Robinson stated that VA should recognize the additional information provided by the Committee in explaining Gulf War veterans' conditions. He stated that this was not apparent at this time, especially in light of the VHI series being so out-of-date.

Chairman Binns suggested asking ORD about the process for making such changes. Dr. Goldberg stated that VA ORD had no control over VA's clinical education. This is under the purview of Dr. Mark Brown's office. Mr. Robinson stated that Dr. Brown had promised him that he was rewriting the VHI Series but that it was unclear what the product would ultimately be, and the issue should be addressed with the Secretary through the 2006 report.

Mr. Smithson noted that the VA had gone out to other bodies in the past, including veterans service organizations, for input on these guidelines. He and Mr. Robinson stated that this issue had been raised several times to VA. Mr. Robinson said that Dr. Brown had admitted at the November 2005 Congressional hearing that review of the guidelines was two years late. Mr. Robinson would like to see the Committee have a guiding hand in this area. Mr. Smithson suggested a letter be drafted to Dr. Brown's office, requesting the status of this review process. Chairman Binns agreed that the Committee could do this. He stated that it wasn't officially part of the Committee's charter as a research advisory committee to address this. However, the Committee has been a focus for veteran comment in this area, because there are no other advisory committees. Dr. Golomb disagreed that this topic was not directly pertinent to the Committee's charter, because VA clinicians would be the ones submitting proposals and they needed to be properly educated on the direction of Gulf War illnesses research.

Chairman Binns asked about ORD's contact with the field investigators. Dr. Goldberg stated that there were monthly voluntary nationwide teleconference calls. He indicated that research administrators generally participated in the calls, not individual investigators. Chairman Binns stated that there was a concern that VA continues to send mixed messages to the field about the latest science in this area. He suggested bringing this issue to Dr. Jonathan Perlin's attention as Dr. Perlin has responsibility over both research and clinical areas.

Dr. Meggs suggested that the Committee provide a copy of the 2004 report to every member of the Institute of Medicine's panel that was reviewing the literature on Gulf War veterans. Dr. Steele said that IOM staff had told her that the report had been included in their review materials. Mr. Robinson stated that they may have reviewed it, but not considered it. Chairman Binns noted that they didn't say this, but rather that the Committee had a different assignment than that of the IOM panel. Drs. Meggs and Golomb stated that they still needed to review the peer-reviewed literature that informed the Committee's report. Chairman Binns stated that this point recently was made, formally and informally, to the chairman of the IOM Committee. It was suggested that she, as chairman, had the authority to expand the scope of the review. She indicated that she would look at whether to consider the DoD pesticide report.

Discussion shifted to future meetings and the possibility of providing an overall review for new Committee members. Mr. Robinson noted that leishmaniasis was becoming a major issue in the current deployment. He thought that it had been underreported in the first Gulf War, and focus should be given to this.

Members discussed the pros and cons of holding meetings outside Washington, DC. It had been suggested that this might increase veteran participation, but there was also a concern that it would limit the ability of senior VA officials to participate in the meetings. Dr. Steele noted that when the Committee did go to another location (East Orange, NJ), no veterans had attended the meeting. Mr. Robinson stated that work could be done to generate veteran interest in particular areas. Dr. Haley commented that the advantage of having VA senior staff present at the Committee's meeting was very important. Unless there was a compelling advantage to going somewhere else, he thought the Committee should continue to meet in Washington, DC. Dr. Meggs agreed. Chairman Binns stated that there was a reason to be in Washington, DC, so there would have to be a better reason for the Committee to meet elsewhere. Mr. Robinson stated that he was thinking along the lines of promoting the Committee's report, and getting its

contents out to the veteran population. He acknowledged that there were, however, more advantages to continued meetings in Washington, DC. He suggested that that there might be a better way to inform the veteran population about the Committee's work. Dr. Steele stated that briefing groups could be held at large VA medical centers across the center. Dr. Golomb suggested a one-page summary page with highlighted points.

Dr. Meggs noted Ms. Nichols' suggestion about holding a Committee meeting in tandem with a medical or scientific meeting. He thought it was a good idea but wasn't sure if those researchers would be interested in attending the Committee's meeting. Chairman Binns suggested presentations given by Drs. Steele and Goldberg at key VA medical centers. Dr. O'Leary stated that this would result in the Committee operating outside of FACA. Dr. Steele suggested that these would be public forums. Dr. Goldberg stated that the Committee's operating funds were for the Committee to meet, discuss and make recommendations. He stated that the funds were not for attending scientific meetings or having individuals go out and represent the Committee. Chairman Binns commented that he understood the general point that Dr. Goldberg was making but that there were instances where this type of activity would be appropriate for Committee staff in the execution of their duties.

Before moving on to Committee discussion, Mr. Smithson reported that the VA General Counsel's office had responded to an earlier question posed by the Committee about members providing expert medical opinions in support of veterans' claims. The General Counsel stated that these expert opinions are not precluded at the regional office and Board of Veterans Appeals levels.

The Committee began discussion of its suggestions for the FY2006 Gulf War illnesses RFA. Dr. Steele stated that Committee staff had, several times previously, assembled lists of bullets outlining research priorities for earlier Gulf War RFAs. These had been based on previous discussions and the Committee's recommendations in the 2004 report. Examples included: autonomic function in ill Gulf War veterans, differences in individual vulnerability to neurotoxins relating to genotype and enzyme levels, use of technologies such as genomic and proteomic methods and imaging technologies, and well-reasoned hypotheses related to other exposures. These areas might be more clearly defined and combined with ideas discussed more recently by the Committee such as an epidemiologic study related to effects of DU exposure or more in-depth research on the prevalence of undetected leishmaniasis.

Chairman Binns stated that the Committee should give as much input as possible during the meeting so that they could hear from members of the public on the ideas expressed. Dr. Haley wondered if it was necessary to adopt a recommended set of priorities for the RFA and give it to VA ORD today. Dr. Steele indicated that was not necessary, and it would be sufficient for Committee members to express their ideas and hold discussion in the meeting today. This information could then be distilled into a document that would be circulated for Committee review and approval before submission as formal recommendations to ORD.

Dr. Golomb suggested circulating the earlier list and inviting suggestions from the Committee. Dr. Steele indicated that there wasn't a single list available that compiled the earlier information, since those items had all been part of various drafts exchanged with ORD for different purposes. Dr. Golomb asked if it would be possible to create a document that incorporates all these recommendations, along with the suggestion of "other objective markers that may be associated with exposures and/or illness." Dr. Meggs asked if anyone had looked at markers of systemic inflammation, e.g., IL-6, or neurogenic inflammation. He suggested that this would be an important area to study.

Mr. Robinson asked whether the public meeting requirements were met by the Committee discussing publicly the basis and type of document it wished to create, then reviewing the specific information and

forming consensus, then coming out with the document. Dr. Goldberg stated that the findings and recommendations needed to be discussed publicly so there could be public input. Chairman Binns stated that the Committee's 2004 report and public discussions at meetings had provided the basis for previous RFA recommendations. These, along with discussions and recommendations made at the current meeting would constitute and help refine the list of recommendations to be offered for the upcoming RFA. He noted that, as discussed during Dr. Steele's presentation the previous day, the weight of available research pointed to neurotoxins such as PB, pesticides, and low-level exposure to nerve agents as being of greater interest than other exposures for the purposes of Gulf War research. Dr. Steele noted that the Committee could identify areas where more information was needed and make a determination of priorities and relevance. She also noted that the Committee's 2004 report contained general topics that the Committee had hoped would be included in previous RFAs, e.g., monitoring the health of Gulf War veterans over time to find out if there are excess rates of MS, Parkinson's' disease, etc. These topics are still important, and could be included in the current RFA.

Dr. Haley summarized areas mentioned as being important for Gulf War research as: (1) autonomic function; (2) predisposing factors, such as enzymes and genes; (3) proteomic and genomic analyses; (4) brain imaging studies; (5) hypotheses on other exposures for which there wasn't much information; (6) immunological studies; (7) birth defects; and (8) health issues for which there is no information, e.g., prevalence of MS or Parkinson's' disease.

Dr. Golomb suggested inclusion of research on the chronic effects of exposures labeled as high priority based on the Committee's previous meeting presentations and discussions. Chairman Binns agreed. While he thought DU, leishmaniasis, etc., should be examined, he indicated that higher priority should be given to exposures that have been shown most consistently to relate to Gulf War-specific effects. It was suggested that studies examining the mechanisms of these exposures be encouraged. Dr. Golomb noted that there may be other exposures that may be important, and these should be followed up as well. However, there are exposures that consistently show up as important, and they are of a particular interest. Dr. Golomb clarified that mechanism studies should focus on: (1) long-term sequelae of these high priority exposures; and (2) mechanisms of persistent or long-term effects of pesticides, PB, etc.

Dr. Haley asked if the Committee wanted to drive the research towards cellular mechanisms versus psychological types of studies, for example, PTSD studies. Dr. Golomb stated that she was afraid that the use of the word "cellular" might be misinterpreted and cause someone to eliminate something that was subcellular or organ-based, e.g. MRS studies. Chairman Binns suggested repeating what the previous RFA said about stress, and inquired if there were any other areas that the Committee thought should not be considered. Dr. Haley wondered whether it might be advisable to suggest there be no more studies focusing on the HPA axis, because this was often a code word for studies of psychological stress. Dr. Steele noted that research in this area could be important since, for example, the literature supported a connection of CFS with adrenal function and many believed HPA axis findings were one of the more promising areas of CFS research. Dr. Golomb suggested that it could be phrased to not include HPA axis studies except in association with its contributory role to effects of other exposures. Dr. O'Callaghan noted that, with respect to inflammatory response in all of the organs potentially involved in Gulf War illnesses, the HPA axis would be involved. Drs. Steele and Golomb agreed.

Chairman Binns asked if there was sufficient reason to jump ahead and anticipate the need for research in some of the areas that the Committee had just agreed should be discussed in 2006. He noted that this might allow researchers who are already looking at areas related to, e.g., inflammation, "to come to the party early." He noted the examples presented by Dr. Steele.

Dr. O'Callaghan commented that instead of looking at different symptoms, exposures and end points, if one read the minutes of previous Committee meetings and reviewed the symptomology and putative mechanisms, one could conclude that the inflammatory process was, in a broad sense, of great importance. He noted that there are end organ changes, certainly in the nervous and immune systems, that could be assessed and indicated that this is a common underlying theme of many of the reported symptoms, e.g., musculoskeletal, pain, allergic response, nervous system response, etc. Alterations in the neuroimmune and neuroinflammatory processes are important. There was information supporting a role for these processes in a variety of different biological systems and these could be studied more accurately with the benefit of animal models. Dr. Steele agreed. She noted that the list of bullets could include, as a priority of interest, studies involving alterations in neuroimmune/neuroinflammatory processes. Drs. Golomb and O'Callaghan indicated that they wouldn't limit it to "neuro" processes. Dr. O'Callaghan stated that there were lots of proinflammatory cytokine mediators within the organs that could not be sampled in living individuals as easily as serum markers. However, these mediators provided the basis for a lot of the different "itises." He mentioned Dr. Mohan Sopori's work that showed an exacerbated inflammatory response in sarin-exposed animals and noted that environmental factors could prime an individual toward an exacerbated inflammatory response, which is not a good thing to have. This could underlie many of the symptoms seen in Gulf War illnesses.

Dr. Steele asked Dr. O'Callaghan how he would summarize this point into a bullet. Dr. O'Callaghan suggested that the RFA seek research that was aimed at investigating the molecular and cellular basis of aberrant responses involving inflammation. Mr. Graves suggested delineating a more specific research bullet to address the neuroimmune and/or neuroinflammatory effects of low dose sarin/cyclosarin exposure with synergistic multicombination concurrent exposures.

Dr. Meggs noted that the problem with leishmaniasis was not exposure, but how the immune system reacts to the exposure. He stated that people who have an aberrant inflammatory response aren't able to clear the organism, and may develop the visceral disease. He believed this was a research area of interest, perhaps using *in vitro* tests to determine whether there was a Th1 or Th2 response. He noted that serology was not a good marker.

Chairman Binns asked whether the main concern, if leishmaniasis was considered an issue, was because it was an undiagnosed infection, i.e., a subclinical infection that is not apparent. Dr. Meggs stated that the question here was whether there is a subset of ill veterans who have a smoldering leishmaniasis infection, which can't be overcome, even though it might be a low level infection. He stated that one possible avenue would be to look at *in vitro* responses to a leishmaniasis challenge, using tests such as a lymphocyte proliferation assay triggered by leishmania antigen. One would test to see if there was a Th1 or Th2 cytokine response. Dr. Golomb noted that some Gulf War studies had included immune challenge tests, but not with regards to leishmaniasis. Dr. Meggs stated that if there was a Th2 response, then this could lead directly to a treatment. Ms. Knox asked if this involved the same principle as allergy shots and Dr. Meggs said it did.

Dr. Golomb asked if the Committee wanted to recommend specific studies in the RFA or specific categories of studies with examples given. Dr. Meggs stated that the lymphocyte challenge study could be built into another leishmaniasis study, an example being the PCR study. He commented that if the individual has cleared the organism and has an immune memory to leishmania, he or she should have a Th1 response. However, if they have a Th2 response that correlates with a PCR identification, they may have a potential problem, but also have a mechanism and suggestion for treatment. Ms. Knox asked if leishmania was cleared from the body completely, or was a chronic infection like *M. tuberculosis*. Dr. Meggs stated that he wasn't sure, but assumed that it was cleared because most people who get it have a self-limiting infection.

Chairman Binns said that another topic that might be included would be research that investigated whether chemicals associated with the high priority exposures or their secondary metabolites were retained in or excreted from the body. Dr. Meggs stated that it was known that organophosphates irreversibly bind to AChE. He asked if there are enzymes in neurons that are neutralized but aren't renewed like AChE. Dr. Haley stated that this depended on how often neurotoxic esterase is renewed, which he didn't know. Chairman Binns noted it would be wonderful to have the Committee's five new members involved in the conversation.

Dr. O'Callaghan noted that Dr. Carrolee Barlow had published a paper that showed that organophosphate delayed neurotoxicity had to be due to something other than neurotoxic esterase binding. He stated that these compounds were very reactive, and could bind to any number of substrates that may or may not be involved in long term illness or symptoms. Dr. Meggs asked if it was true that the mechanism of encephalopathy after organophosphate poisoning was not known and Dr. O'Callaghan confirmed this.

Dr. Steele asked how these ideas could best be captured into a succinct bullet and suggested that it might be worded along the lines of encouraging research investigations that look at retention of toxins or secondary metabolites that indicate prior exposure. Dr. Meggs mentioned earlier information presented to the Committee about work done at Lawrence Livermore Laboratories using MR-spectroscopy to detect very small levels of toxins.

Dr. Haley commented that it was important to recommend that all human studies of Gulf War illnesses utilize well-constructed case definitions. He pointed out that some of the studies were simply asking for volunteers, as opposed to including participants who meet criteria for a well-constructed case definition. Dr. Golomb stated that a case definition should not be specified until the mechanisms underlying these conditions were better known and that the mechanisms should define what a case is. Dr. Haley clarified that the researchers should be clear that they are using a case definition and describe what it is, but that a preferred case definition wouldn't be prescribed by the Committee. It was important that the study sample not be a group of volunteers and utilization of a well-constructed case definition should be a review parameter of study proposals. Dr. Steele stated that this might drive everyone to the Fukuda case definition, but agreed this was better than a list of volunteers who say they are sick.

Mr. Graves requested that a bullet be included regarding low-dose mustard gas exposure or mustard gas secondary metabolites. Dr. Golomb commented that mustard gas exposure was rare in the first Gulf War. Dr. Haley noted that Czechoslovakian troops had detected mustard gas in ambient air. Mr. Graves described an event in which he had been involved when a substance identified as mustard gas had hit his unit and others. Dr. Steele asked Mr. Graves if he was confident that he was exposed to mustard gas, since some of the symptoms he described suggested that other exposures might have been involved. Mr. Graves stated that he thought it was mustard gas. He noted that mustard was used in chemotherapy, which stops the growth of fast growing cells and that his hair fell out after this exposure. Dr. Golomb noted that hair can fall out after any major stress due to a phenomenon known as telogen effluvium. She indicated that she had heard of only one or two US soldiers being exposed to mustard gas during the Gulf War. Mr. Robinson commented that DoD verified one case of mustard gas exposure (PFC Fisher). With respect to the Czech mustard gas detection he said that DoD had concluded that it had been due to a fatty substance in the sampler that skewed the data. Coincidentally, he was contacted recently by a researcher who will be investigating a known mustard gas exposure in Iran. This study is being conducted though the NIH, and will be looking at the health outcomes of this particular exposure. He offered to put Mr. Graves in contact with this researcher.

Chairman Binns asked if it was being suggested that the gas that may have affected Mr. Graves' unit was not mustard gas, but perhaps sarin or cyclosarin. Dr. Golomb stated that mustard gas was a desiccant, and acted in a very different way than the substance described by Mr. Graves. Dr. Meggs suggested that low-dose mustard gas exposure may have different effects. Dr. Steele suggested that an option might be to recommend research on populations with known low-level exposure to chemical weapons (sarin, mustard, etc.) to investigate the long term sequelae of these exposures. Mr. Robinson noted that mustard shells had been found and could have been destroyed in demolition operations.

Chairman Binns commented that this discussion had been productive and Dr. Haley added that a good list of research priorities had been assembled. Dr. Steele agreed and indicated that the discussion had provided the information needed to put together the recommendations and that a draft document would be circulated for Committee review. (See Appendix B for final document.)

Public comment – Day 2

Chairman Binns invited members of the public to provide comments.

Ms. Denise Nichols submitted a letter provided by Ms. Julia Dykman, which had been submitted to the Shays Congressional hearing in November 2005. Ms. Nichols discussed results of a test that Ms. Dykman had recently taken that identified several heavy metals in Ms. Dykman's samples. She indicated that Ms. Dykman was willing to share these test results with the Committee. Ms. Knox inquired as to Ms. Dykman's location during the Gulf War. Ms. Nichols replied that Ms. Dykman served out of the hospital at Al Jubayl. Chairman Binns noted that the Committee had a general recommendation related to markers and that it could consider modifying it to include the possibility of investigating heavy metals. Dr. Haley asked if this was a type of chelation therapy or test. Ms. Nichols said no, that it involved special methods to pull out more heavy metal for testing. She stated that it was something that should be looked into, and suggested it may be a marker for inflammation.

Ms. Nichols circulated information about DoD-supported Gulf War research being done at Wright State University. One aspect of this research was the identification of a marker for predisposition to Gulf War illnesses. Ms. Nichols stated that she had been a participant in this research and shared her results with the Committee. Dr. Steele thanked Ms. Nichols and indicated that Committee staff was aware of the Wright State program and hoped to provide information on this research to the Committee.

Ms. Nichols suggested that research protocols require veterans to identify their unit, location and/or job in the military during the Gulf War. She stated that this requirement should be included in the guidelines for the research process. Ms. Nichols also suggested that research related to viral infection markers and subsequent treatment was very important. She commented that several Gulf War veterans received the polio vaccine, and it should be considered in the synergistic mix of exposures.

Ms. Nichols commented that an organophosphate marker study might be critical research for Gulf War veterans. This type of research might identify individuals who need to take special precautions to avoid future organophosphate exposures. She added that the ALS/MS/Parkinson's disease research should determine whether Gulf War veterans were experiencing atypical cases when compared to the general population.

Ms. Nichols asked that the draft resulting from the Committee's discussion of RFA topics be put on the Committee's website. Chairman Binns asked that Ms. Nichols relay to other veterans that this did not

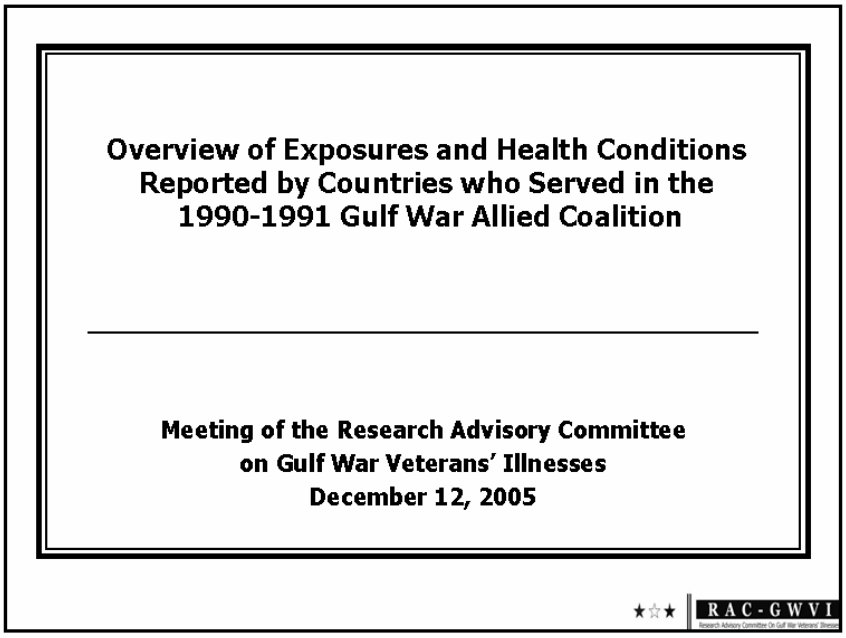
have to be a consensus process, and that they could communicate any ideas they have that were relevant, regardless of whether the Committee's draft was posted or not.

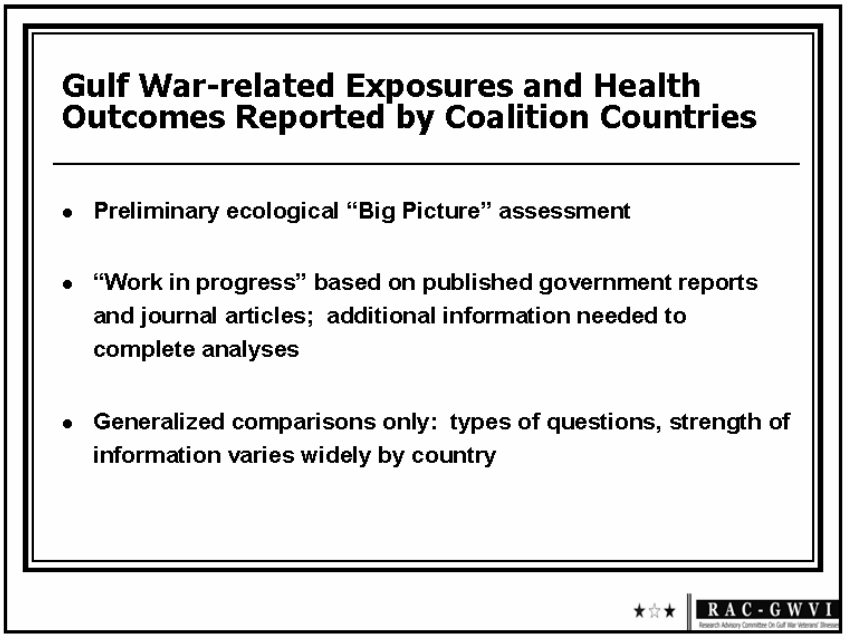
Chairman Binns thanked everyone present for a good meeting and thanked VA ORD staff for their participation. Mr. Robinson thanked Committee staff for its hard work.

Chairman Binns adjourned the meeting at 1:10 p.m.

Appendix A

Presentation 1 – Barbara LaClair





The Allied Forces Coalition

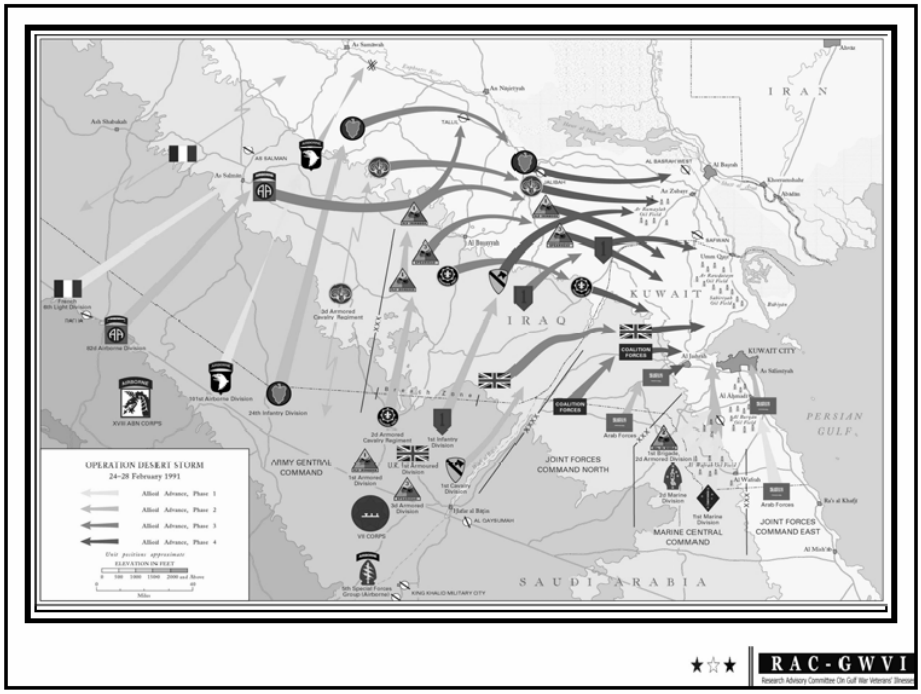
- 38 countries in addition to U.S.
- Slightly more than 200,000 troops
- Members of the Coalition included Argentina, Australia, Bahrain, Bangladesh, Belgium, Canada, Czechoslovakia, Denmark, Egypt, France, Germany, Greece, Italy, Japan, Kuwait, Morocco, Netherlands, New Zealand, Niger, Norway, Oman, Pakistan, Poland, Portugal, Qatar, Saudi Arabia, Senegal, South Korea, Spain, Syria, Turkey, United Arab Emirates, United Kingdom and the United States.
- Germany and Japan provided financial assistance instead of military aid.
- Israel remained officially neutral.

★☆★ RAC-GWVI

United Kingdom

- Approximately 53,000 deployed
  - 70% Army
  - 11% Navy
  - 19% Air Force
- Forces concentrated closer to Saudi / Kuwait border

★☆★ RAC-GWVI



United Kingdom: Health Studies

- Unwin et al, 1999
  - Cross-sectional postal survey
  - 4,248 GWV; 4,250 Bosnia vets; 4,246 NGW era vets
  - Aug 1997-Nov 1998
- Cherry et al, 2001
  - Cross-sectional questionnaire
  - 9,585 GWV; 4,787 NGW era vets
  - Dec 1997-Sept 1999

RAC-GWVI

United Kingdom: Exposures

Pesticides	69.2 % used personal insecticides 34.4% used > 14 days 20.1% in sprayed quarters 38.4% on clothing, bedding DEET for skin application Permethrin for clothing, mosquito netting, area spray Locally purchased azamethipos pesticides for flies Malathion for de-lousing

★☆★ RAC-GWVI

United Kingdom: Exposures

Nerve Agents	70-82% wore protective gear/ heard alarms
PB/NAPs	81.6% reported use 65.1% > 14 days
Vaccines	Anthrax 57-75% (pertussis adjuvant) Plague 25.7% Typhoid 12.5% Cholera 13.7%

★☆★ RAC-GWVI

United Kingdom: Exposures

Oil Fires	61-72% reported smoke exposure
Depleted Uranium	No data
CARC paint	No data

★☆★ RAC-GWVI

United Kingdom: Health Symptoms

- Current symptoms (past month):

Symptom	% in GWV	Excess Prev	Adj. OR
Fatigue	50.7%	23.0%	2.7*
Headache	53.5%	17.9%	2.1*
Memory problems	44.9%	27.8%	4.2*
Muscle/joint/musculosk. pain	40.0%	16.5%	2.8*
Diarrhea	NR		
Dyspepsia/indigestion	NR		
Skin problems	NR		
Shortness of breath	NR		

★☆★ RAC-GWVI

United Kingdom: Health Conditions

- Conditions seen, diagnosed or treated by physician (s/r):

Complaint/ Condition	% in GWV	Excess Prev	Adj. OR
Skin condition (dermatitis)	21.3%	9.0%	1.5*
Arthritis/ joint problem	9.7%	1.8%	1.4*
GI problems	NR		
Respiratory problem (asthma)	6.5%	1.8%	1.8*
CFS	3.3%	3.0%	4.2*
PTSD	13.2%	9.1%	3.8*
CMI	61.9%	25.5%	2.9*

★☆★ RAC-GWVI

United Kingdom: Summary

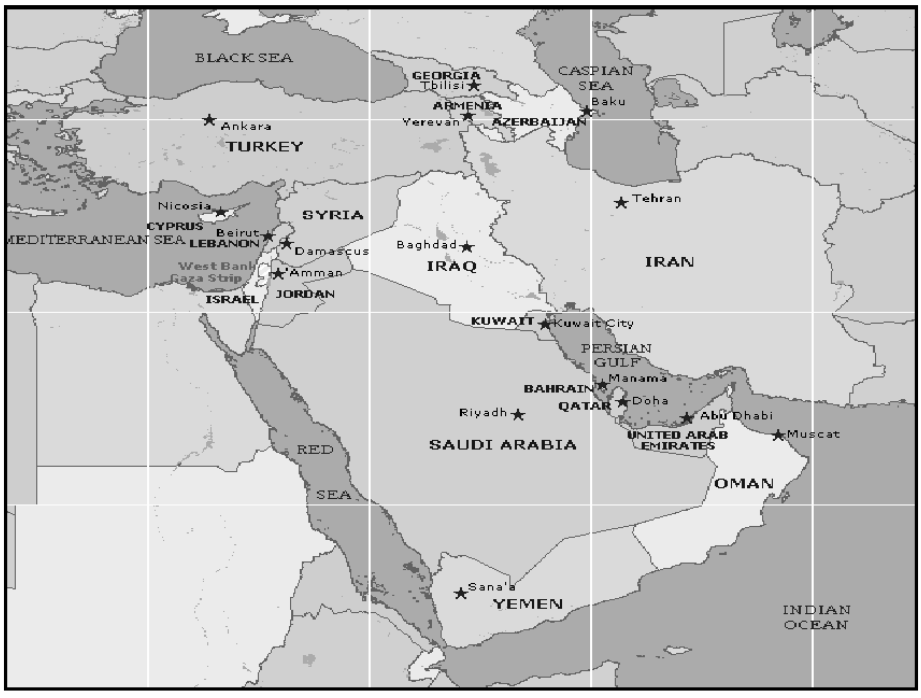
- GW cohort reported symptoms & disorders more frequently than Bosnia and Era cohorts
- Majority of exposures associated with all outcomes
- Vaccination against biological warfare & multiple routine vaccination associated with CMI

★☆★ RAC-GWVI

Canada

- Approximately 4,447 troops deployed
  - 27% Army
  - 33% Navy
  - 40% Air Force
- August 1990 to July 1991
- Diverse locations, including Cyprus, Iraq, Kuwait, Saudi Arabia
- 2 largest contingents in naval blockade and air war
- Operated 1 field hospital
- Minimal involvement in ground conflict

★☆★ RAC-GWVI



Canada: Health Studies

- *Health Study of Canadian Forces Personnel Involved in the 1991 Conflict in the Persian Gulf*, Goss Gilroy, Inc., April 1998
- Cross-sectional survey, all Canadian GWVs
- Conducted in 1997
- Postal questionnaire
- Comparison group of Canadian Forces members serving in other locations at time of Gulf War
- Results also compared to OHS study of population health

★☆★ RAC-GWVI

Canada: Exposures

Pesticides	Minimal exposure. Approximately 20% ever used DEET Permethrin use rare
Nerve Agents	Not reported.
PB/ NAPs	85% reported use. Duration varied from 3 days to 4 weeks.
Vaccines	Few received anthrax. Indiv. serving with 1st Canadian Field Hospital received plague and anthrax vaccine with pertussis adjuvant.

★☆★ RAC-GWVI

Canada: Exposures

Oil Fires	Minimal exposure
Depleted Uranium	Troops rarely inside destroyed Iraqi vehicles, and then usually weeks after destruction.
CARC paint	Few individuals involved with painting vehicles.

★☆★ RAC-GWVI

Canada : Health Symptoms

- Symptom checklist of 37 symptoms, matching list used by U.S. CCEP program
- Symptom report data aggregated to "combined symptom clusters", similar to those in Iowa Persian Gulf Study
- Findings generally comparable to those of Iowa study, except for higher rates of cognitive dysfunction, CFS, and depression among Can. GW vets

★☆★ RAC-GWVI

Canada: Summary

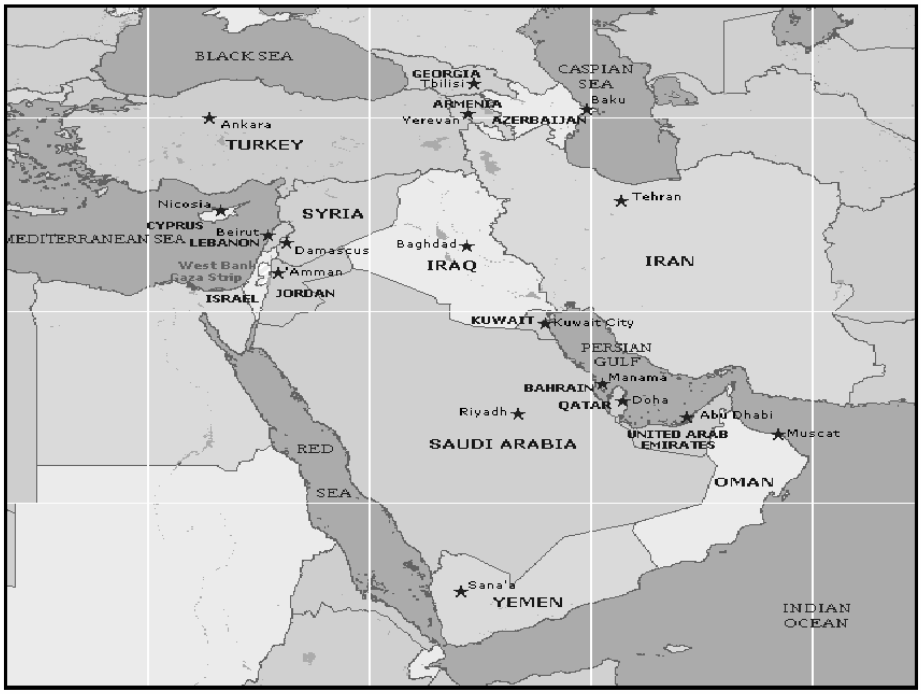
- Prevalence of chronic health problems among NGW control group similar to that of general population
- GWVs had higher prevalence of most conditions, esp. diseases of bone & joints, allergies, stomach problems
- Symptoms of cognitive dysfunction, CFS, MCS showed largest differences from controls (adj. PORs = 4 - 5)
- Cognitive dysfunction most strongly associated with psych stressors (POR 2.1), physical trauma (POR 1.5) and CNS exposure factors (POR 1.5)
- Provider-diagnosed PTSD associated with psych stressors (POR 5.8), chemical warfare agents (POR 5.3), CNS factors (POR 3.0)

★☆★ RAC-GWVI

Australia

- Approximately 1,900 deployed
  - 6% Army
  - 87% Navy
  - 7 % Air Force (transport & logistic support only)
- Majority of troops located on-ship in Gulf of Oman

★☆★ RAC-GWVI



Australia: Health Studies

- ***Australian Gulf War Veterans' Health Study*, Prof. Malcolm Sim, 2003**
  - Cross-sectional survey of all 1,873 GW veterans
  - Postal questionnaire and medical evaluation
  - Recruitment ended April 2002
  - Comparison group of era ADF personnel, eligible for deployment but non-deployed
- **Kelsall HL *et al*, 2004**

★☆★ RAC-GWVI

Australia: Exposures

Pesticides	26% used personal pesticides 20% lived where pesticide sprayed/ fogged 11% applied pesticides 5% clothing/ uniforms treated with pesticides 3% tent treated with pesticides (permethrin) 0.4% wore flea collar Army used Dieldrin (OCl); Malathion, Diazanon, Temephos (OP); Baygon,Bendiocarb (Carbamates). Clothing & tents dipped in permethrin & dried. DEET-based insect repellants issued.
Nerve Agents	46% used NBC suits 11% in area where chemical warfare used

★☆★ RAC-GWVI

Australia: Exposures

PB/ NAPs	51.4% reported use; 17% took >180 pills
Vaccines	15.3% reported anthrax vaccine (not on official schedule) 48.1% reported plague vaccine 14% reported >5 immunizations w/in 1 week Routine vaccines included typhoid, cholera
Oil Fires	54% SMOIL exposure
DU	19.3% handled DU shell casings

★☆★ RAC-GWVI

Australia: Exposures

CARC paint	Exposure unlikely 1.3% self-reported exposure
Sand	48% exposed to dust storms
Fuels	79% solvents, oils, diesel, fuels on skin 78% refueling
Food/Water	57% ate locally sourced military food 41% drank water from local taps/ wells 15% showered with water with fuel in it 12% drank water with oil in it

★☆★ RAC-GWVI

Australia: Health Symptoms

- Current symptoms (past month):

Symptom	% in GWV	Excess Prev	Adj. OR
Fatigue	66%	10%	1.6*
Headache	61%	7%	1.3*
Memory problems	46%	12%	1.7*
Muscle/joint/musculosk. pain	39%	5%	1.3*
Diarrhea	26%	9%	1.7*
Dyspepsia/indigestion	28%	5%	1.4*
Skin problems (rash, irritation)	36%	8%	1.5*
Shortness of breath	31%	9%	1.6*

★☆★ RAC-GWVI

Australia: Health Conditions

- Conditions seen, diagnosed or treated by physician (s/r):

Complaint/ Condition	% in GWV	Excess Prev	Adj. OR
Skin condition (any other)	16%	4%	1.4*
Arthritis/ joint problem	22%	2%	1.2
GI problems	11%	1%	1.1
Respiratory problem (asthma)	4%	1%	1.2
CFS	1%	0%	0.8
PTSD	5%	3%	3.1*
CMI	NR		

★☆★ RAC-GWVI

Australia: Summary

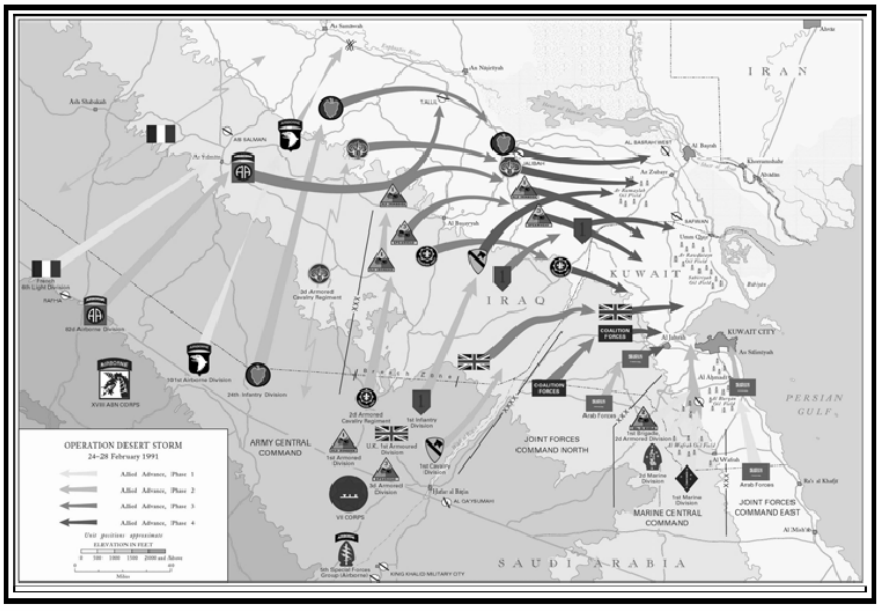
- GWVs reported all general health symptoms more frequently than NGVs, more likely to report higher number of symptoms, greater symptom severity
- Rates of psychological disorders (PTSD, anxiety, depression, substance abuse) higher among GWV than comparison group
- Weak associations between neurological symptoms and # of immunizations, exposures to PB, anti-malarials, anti-biologicals, solvents, pesticides, repellants (Adj. ORs 1.1-1.9)

★☆★ RAC-GWVI

France

- **Approximately 21,000 deployed**
  - 62% Army
  - 23% Air Force
  - Other – Navy, Medical Services, Fuel Services
- **Troops located primarily on western flank**

★☆★ RAC-GWVI



★☆★ RAC-GWVI

France: Health Studies

- ***The French study on the Gulf War and its impact on health*, Prof. R. Salamon, July 2004**
- **Cross-sectional study of all French military and civilian personnel who served in Gulf War**
- **Conducted from October 2001 to June 2004**
- **Postal questionnaire; free medical exams offered**
- **5,666 questionnaires;1008 medical exams**
- **No comparison group**

★☆★ RAC-GWVI

France: Exposures

Pesticides	25% reported contact 14% used personal insecticides No Organophosphates DEET for personal repellant K-orthrin on mosquito netting Lindane on ground, sprayed tents & buildings Pyrethrins for pest control on aircraft No systematic spraying of aerosols
Nerve Agents	63% experienced at least 1 alert

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France: Exposures

PB/NAPs	31% reported use Relied more on protective gear – tropical suits & ventilated shelters
Vaccines	No anthrax, botulinum Did receive plague, typhoid

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France: Exposures

Oil Fires	28% reported smoke exposure
Depleted Uranium	No data
Petrochemicals	No data
Food/water	Relied on bottled water. Some reports of drinking bottled water from Iraqi stock, water transported in fuel tanker trucks

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France: Health Symptoms

- Checklist of 49 symptoms, experienced at any time since return from Gulf War
- No estimates of current symptom prevalence
- Reported symptom rates not comparable to other countries

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France: Health Conditions

- Conditions seen, diagnosed or treated by physician, since return from Gulf (s/r):

Complaint/ Condition	% in GWV	Excess Prev	Adj. OR
Skin condition	8%		
Arthritis/ joint problem	NR		
GI problems	11%		
Respiratory problem	14%		
CFS	NR		
PTSD	0.2%		
CMI	NR		

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France: Summary

- Lack of current prevalence and comparison groups limit interpretation of symptom and condition reports
- No evaluation of associations between exposures & health outcomes
- 89% of study participants reported current health status as very good or good
- 150 GW veterans have applied for pensions:
  - 61 denied
  - 38 pending
  - 51 approved
    - 24 GW service connected

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Denmark

- Total of 821 served between August 1990- December 1997
  - About 60% deployed from 1992-1994
  - Troops successively replaced every 6 months
- Deployed primarily in peace-keeping and humanitarian operations after war
- 29-member surgical team deployed with British hospital in Al Jubayl

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Denmark: Health Studies

- Danish Gulf War Study, Ishoy, Suadicani *et. al*, 1999
- Cross-sectional study, Jan 1997- Jan 1998
- 686 GW veterans, 400 non-deployed controls matched on age, sex, profession
- Symptom & exposure questionnaires, health examinations

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Denmark: Exposures

Pesticides	26.9% lotions/sprays for fleas 19.5% insecticides for cockroaches
Nerve Agents	0.4% nerve gas 0.3% mustard gas or similar 4.0% SCUD explosions w/in 2 km
PB/NAPs	Unknown
Vaccines	Unknown

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Denmark: Exposures

Oil Fires	45% fumes from burning wells
Depleted Uranium	3% reported DU exposure 54% inside destroyed Iraqi tanks
Petrochemicals	64% diesel, kerosene other fuels 57% skin contact 34% evaporated diesel on ground
Food/water	77% ate local foods 16% bathed/drank contaminated water (chemical, pesticides)

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Denmark: Health Symptoms

- Current symptoms (past 12 months, onset during/after GW):

Symptom	% in GWV	Excess Prev	Adj. OR
Fatigue	26.4%	15.6%	3.0*
Headache	19.2%	12.7%	3.4*
Memory problems	31.2%	23.0%	5.1*
Muscle/joint/musculosk. pain	9.2%	(-1.6%)	0.8
Diarrhea	17.2%	13.3%	5.1*
Dyspepsia/indigestion	16.9%	9.1%	2.4*
Skin problems¶	17.1%	11.9%	3.8*
Shortness of breath	14%	10.5%	4.5*

¶ lifetime prevalence

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Denmark: Health Conditions

- At clinical examination, significantly larger proportion of GW veterans had one or more ICD-10 diagnoses (80.8% vs. 71%, p=0.002)
- 38% of GW veterans had one or more diagnoses that could be related to service in Gulf

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Denmark: Summary

- Except for muscle/joint symptoms, symptom patterns similar to U.S., U.K veterans
- Higher symptom prevalence among GWV was seen for symptoms with onset since GW; prevalence prior to August 1990 was similar to NGV group
- Neuropsych symptoms associated with:
  - Bathe in /drink contaminated water OR=5.0 (2.9-8.9)
  - Exposure to DU OR=4.2 (1.4-13.0)
  - Contact with dead animals OR=1.4 (1.1-1.8)
  - Burning waste/ manure OR=1.8 (1.1-2.9)
- GI symptoms associated with:
  - Burning waste/ manure OR=2.5 (1.3-5.0)
  - Insecticide against cockroaches OR=2.3 (1.2-4.4)

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Czechoslovakia

- 367 troops deployed (169 in Phase I, 198 in Phase II)
- Primarily conducted CW agent detection
- Located in Kuwait & Saudi Arabia

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Czechoslovakia: Studies

- Czech government conducted 2 studies of health of Gulf War veterans
- 198 veterans ordered to undergo yearly health exams

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Czechoslovakia: Exposures

Pesticides	Unknown
Nerve Agents	Czech detection teams reported chemical alerts Jan 19, 1991 and Jan 24, 1991
PB/NAPs	Not used
Vaccines	Broad array of vaccinations No inoculations for Anthrax
Oil Fires	No data
Depleted Uranium	No data

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Czechoslovakia: Health Outcomes

- "Studies found no similarity between symptoms reported by Czech veterans and U.S. veterans" (GulfNEWS, January 26, 1998)
- SIU Report (1998) – Czechs examined 86% of GW veterans residing in Czech Republic:
  - 40% in good health
  - Most frequent complaints fatigue, headaches, joint pain
  - No objective explanation of illness in 6 veterans (4.5%), but not attributed to Gulf War service

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Arab Coalition

- Saudi Arabia ~ 45,000
- Egypt ~ 35,000
- Syria ~ 20,000
- Kuwait, Bahrain, UAE, Oman, Qatar ~ 17,000
- Pakistan ~ 5,000
- Morrocco ~ 1,500
- Also Hungary and Slovakia

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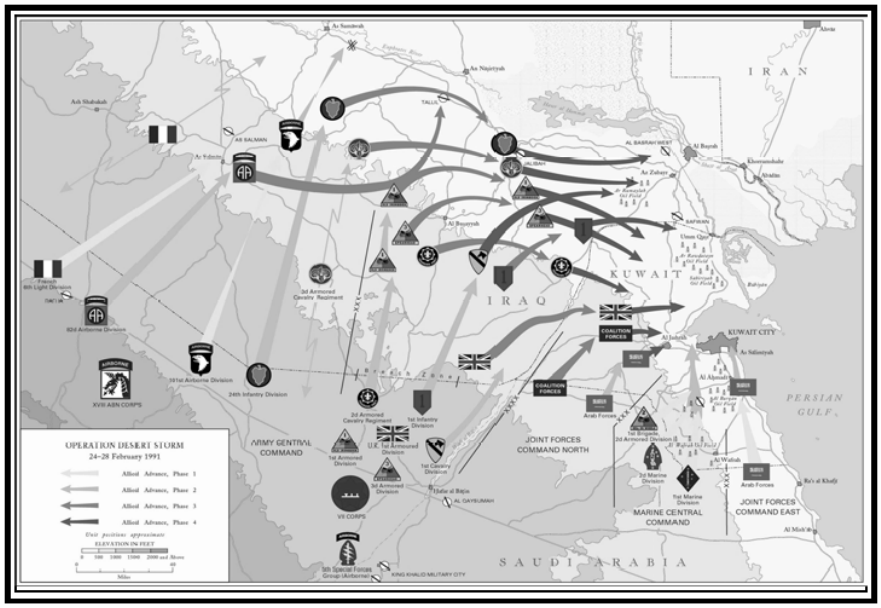

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Arab Coalition: Studies

- Gackstetter et al, 2005
  - Hospitalizations of Saudi Arabian National Guard veterans, 1991-1999
  - 8,342 soldiers exposed to combat at Al Khafji, compared to 7,270 soldiers in Riyadh area

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Arab Coalition: Exposures

- No Data

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Arab Coalition: Health Outcomes

- Gackstetter study:
  - Slight increase in hospitalizations among combat group RR=1.80, (95% CI 1.25-2.59)
  - No unusual patterns of diagnosis found
- "Middle Eastern countries have not reported unusual health problems in their military populations. Early concerns about respiratory disorders that might be related to oil well fires had not been substantiated." Gulf War Review, May 2001

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Summary: Excess prevalence of symptoms

Symptom	U.S.	U.K.	Can	Austr	Den
Fatigue	23%	23%		10%	16%
Headache	17%	18%		7%	13%
Memory problems	32%	28%		12%	23%
Muscle/joint pain	18%	17%		5%	(-2%)
Diarrhea	16%			9%	13%
Dyspepsia/indigestion	12%			5%	9%
Skin problems	16%			8%	12%
Shortness of breath	13%			9%	11%

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Summary: Excess prevalence of conditions

Condition	U.S.	U.K.	Can	Austr	Den
Skin condition	20-21%	21%	4- 7%	4%	
Arthritis/ joint problem	6-11%	10%	-1 – 3%	2%	
GI problems	15%		5- 7%	1%	
Respiratory problem	4-7%	2%	2- 5%	1%	
CFS	1-4%	3%		0%	
PTSD	3-6%	9%	6%	3%	
CMI	13-25%	26%			

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Summary: Allied Coalition Exposures

Pesticides	U.S.	U.K.	Can	Aust	Fr	Den
Any Contact	44-63%		Minimal		25%	
Personal pesticide	48%	69%	20%	26%-37%	14%	27%
On clothes, bedding		38%		5%		

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Summary: Allied Coalition Exposures Types of pesticides & repellants used

Category	U.S.	U.K.	Can	Aust	Fr	Den
OP	Azimethipos Chlorpyrifos Diazanon Dichlorovos Malathion	Azamethipos Malathion	?	Malathion Diazanon Temephos	None	?
OCl	Lindane	?	?	Dieldrin	Lindane	?
Carbamate	Bendiocarb Methomyl Propoxur	?	?	Baygon Bendiocarb	?	?
Pyrethroids	Permethrin d-phenothrin	Permethrin	Permethrin	Perigan	Pyrethrins K-orthrin	?
Repellants	DEET	DEET	DEET	DEET	DEET	?

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Summary: Allied Coalition Exposures

Nerve Agents	U.S.	U.K.	Can	Austr	Fr	Den
Heard alarms/ wore gear	56-72%	70-82%	?	46%	63%	
Nerve gas	5-12%					0.4%
Near SCUD explosion	43%					4%
PB/NAPs						
Used PB	42-49%	82%	85%	51%	31%	?
Duration/freq		65% >14d	3d-4wk	17%> 180 pills		

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Summary: Allied Coalition Exposures

Vaccines	U.S.	U.K.	Can	Austr	Fr	Den
Anthrax	41%	57-75%	Few	15%	0%	?
Plague	22%	26%	Some	48%	Routine	?
Typhoid	59%	13%	Routine	Routine	Routine	?
Cholera	0%	14%	0%	Routine	?	?
Botulinum	12.5%	0%	0%	0%	0%	?

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Summary: Allied Coalition Exposures

	U.S.	U.K.	Can	Austr	Fr	Den
Oil Fire Smoke	65%	61-72%	Minimal	54%	28%	45%
DU	2-10% ?	8-10%	Minimal	19% handled DU shell casings	?	54% inside destroyed Iraqi vehicles
CARC paint	21%	18-46%	Minimal	1.3%	?	?

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Summary: Health Outcomes

- When compared to non-deployed controls, GWV consistently report higher rates of symptoms and health conditions
- US & UK- GW vets have similar patterns of health symptoms and conditions
- Denmark - similar for GI, respiratory, skin. Somewhat lower in neuro symptoms, lower in musculoskeletal
- Australia – lower overall
- Canada – may be similar to US & UK, but not clear
- France - may be less ill, but not clear

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How do illness patterns relate to exposures?

What exposures do the US & UK have in common, for which Denmark *may* be different, and Australia *is* different and France *is* different?

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Summary: Allied Coalition Exposures

Pesticides	U.S.	U.K.	Den	Austr	Fr
Use	≈	≈	↓	↓	↓↓
Types used					
OPs	YES	YES	?	YES	NO
OCI	YES	?	?	YES	YES
Carbamate	YES	?	?	YES	?
Pyrethrins	YES	YES	?	YES	YES
DEET	YES	YES	?	YES	YES

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Summary: Allied Coalition Exposures

Exposure	U.S.	U.K.	Den	Austr	Fr
Chemical weapon alerts/exposures	≈	≈	↓↓	↓	≈
PB	≈	↑	?↓	≈	↓
Vaccines					
Anthrax	≈	↑	?	↓↓	No
Plague	≈	≈	?	↑	Routine
Botulinum	Yes	No	No	No	No
Oil Fires	≈	≈	↓	↓	↓↓
DU	Poor Data				
CARC	≈	≈	?	↓↓	?

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Summary Overview

- US & UK
  - Similar in all symptoms, conditions
  - Similar in rate of pesticide use, types of pesticides
  - Similar reported s/r exposures to nerve agents, oil fires, plague vaccine
  - UK > US on PB use, anthrax rate (pertussis adjuvant)

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Summary Overview

- Denmark
  - Similar to US and UK in GI, respiratory, skin; somewhat less in neuro; much less in musculoskeletal symptoms
  - Primarily peace-keeping role after cease-fire
  - Lower rates of pesticide use, types unknown
  - Much lower rates of s/r exposure to nerve agents
  - Somewhat less exposure to oil fires
  - PB use unlikely (but unknown)
  - Vaccines unknown

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Summary Overview

- Australia
  - Lower rates of excess health problems overall
  - Lower rates of pesticide use, but similar types
  - Lower rates of exposure to nerve agents
  - Lower rates of anthrax vaccination
  - Less exposure to oil fires
  - Frequency of PB use similar to U.S.

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Summary Overview

- France
  - Possibly fewer health problems
  - Lower rates of pesticide use, no OPs , ? carbamates, others similar types
  - Similar rates of s/r chemical alerts
  - Less use of PB
  - No anthrax vaccination
  - Less exposure to oil fires

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Preliminary Conclusions

- US and UK, with highest rates of excess illness, are distinguished from other nations by higher rates of pesticide use, use of anthrax vaccine, and somewhat higher rates of exposures to oil fire smoke and reported chemical alerts
- France, with possibly the lowest illness rates, had lower rates of pesticide use, no use of organophosphate pesticides, no use of anthrax vaccine
- Relationships between PB use and illness rates are unclear

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Presentation 2- Lea Steele

RAC 2006 Report:

Overview of Materials Considered in 2004-2005

Lea Steele, Ph.D.

December 12, 2005

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December 12-13, 2005
A Working Meeting

- Review, summarize information on topics covered in 2004-2005 RAC Meetings
- Outline findings and recommendations in key areas
- Synthesize, compare strength of evidence for each exposure in relation to Gulf War illnesses

RAC 2006 Report

- Findings, recommendations re: topics reviewed in 2004 and 2005
- Update on topics covered in 2004 RAC Report
- Synthesis and analysis of findings, identification of research priorities

Areas Addressed in 2004 RAC Report

- Nature and prevalence of Gulf War illness symptom complex
- Urgent need for treatments for GWI
- Evidence of neurological pathology in Gulf veterans
- Links between GWI and neurotoxic exposures
- Possible links with other exposures
- Birth defects and health of family members
- Need for coordination of federal data resources
- GWI research relates to current deployments, domestic security
- Focus, funding of federal GW research programs

Diverse sources of research information considered ....

- *Published research*
  - Epidemiologic studies of Gulf War-era veterans
  - Clinical studies of Gulf War veterans
  - Occupational health studies related to exposures
  - Animal studies
  - Cell culture studies
- *Research-in-progress*
- *Government reports*
  - Various agencies (e.g. DOD, VA, HHS, GAO)
  - Various committees (e.g. Congressional, PAC, PSOB, NIH)
  - Foreign governments
  - Topics related to exposures (measured and modeled), health risk assessments
- *Nongovernmental reports*
  - IOM
  - RAND
  - Other

Major Topics Covered in 2004 and 2005 RAC Meetings

- Depleted uranium
- Oil well fires, combustion products
- Particulates
- Fuel exposures
- Solvents, CARC paint
- Vaccines
- Infectious diseases

- Chronic multisymptom illnesses in the general population
- Epidemiologic studies of multisymptom illness in Gulf veterans
- Respiratory conditions
- Cancer
- Immunological, neurological findings in Gulf veterans

- Treatments
- VA Research Programs

RAC 2006 Report

- Findings, recommendations re: topics reviewed in 2004 and 2005
- Update on topics covered in 2004 RAC Report
- Synthesis and analysis of findings, identification of research priorities

Review of 2004-2005 Exposure Topics

- Review highlights of information presented
- Summarize what is known/not known in each area in relation to Gulf War veterans' health
- Discuss findings, recommendations

2004-2005 Exposure Topics

- Depleted uranium
- Oil well fires, combustion products
- Particulates
- Fuel exposures
- Solvents, CARC paint
- Vaccines
- Infectious diseases

Depleted Uranium

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Major Reports on the Health Effects of DU

- RAND (1999)
- IOM (2000)
- Royal Society (UK, 2002)
- USACHPPM

Major Reports on the Health Effects of DU: General Conclusions

- **Chemical (heavy metal) toxicity of greater concern than radiological effects of DU**
- **Concern about increased cancer risk**
  - Minimal concern re: possible increase in overall cancer risk (primarily lung)
  - Occupational studies of uranium exposures often too small to provide information re: less common cancers
- **Concerns about renal toxicity**
  - Transient effects demonstrated, but minimal concern re: longer-term kidney effects except with large exposures (e.g., Gulf veterans with significant amount of embedded shrapnel)
  - Solubility of uranium affects outcomes in animal studies
- **Little research available re: possible damage to other systems and organs (cardiovascular, hematological, respiratory, neurological, immunological, etc)**

Depleted Uranium: Information Considered by RAC in 2004-2005

- Efforts to estimate levels of DU exposure
- Animal studies to evaluate effects of DU exposures via different routes, in different systems
  - Ingested, injected
  - Embedded pellets
  - Inhaled
- Epidemiologic studies to evaluate associations between DU exposure and health outcomes in Gulf War veterans

Estimates of Exposure/ Modeled Health Risks

Depleted Uranium

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DU Exposure: OSAGWI Report

DOD has identified 3 levels of DU exposure in Gulf War veterans

- Level 1: ~ 150 people with high exposures associated with friendly fire incidents and rescue
- Level 2: ~ 750 people exposed during cleanup operations following the Doha fire, and cleanup of destroyed U.S. vehicles
- Level 3: unknown numbers exposed to smoke from Doha fire, burning U.S. and Iraqi tanks, entered DU-contaminated equipment

Preliminary Assessment of DU Munitions Health Effects.

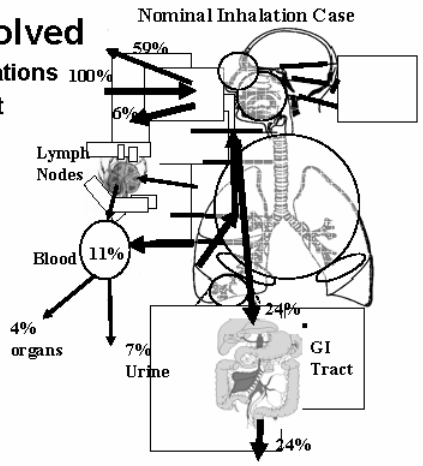
Al Marshall

National Security Studies Department
Sandia National Laboratories
Presented to RAC Gulf War Veteran's Illness
Washington DC
February 24, 2004

Slide adapted from: Marshall A. Preliminary assessment of depleted uranium munitions health effects. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Feb 24, 2004; Washington, DC.

Basic distribution of inhaled DU.

- **Basic equations solved**
  - **Coupled differential equations**
  - **Compute time-dependent**
    - Transport
    - Blood absorption
  - **Each compartment**
  - **Rapid and slow blood**
- **Equations couple to**
  - **Other organ models**
  - **Urine elimination**



Slide adapted from: Marshall A. Preliminary assessment of depleted uranium munitions health effects. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Feb 24, 2004; Washington, DC.

Preview of Preliminary Findings.

- Inhaled DU mass exceeds DoD estimates
- Fragment dose contribution significant
- DU radiological effect insignificant
- DU in Kidney high for max case, chemical heavy metal: consequences uncertain
- Other DU heavy metal effects possible, significance uncertain

Slide adapted from: Marshall A. Preliminary assessment of depleted uranium munitions health effects. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Feb 24, 2004; Washington, DC.

Depleted Uranium
CAPSTONE Aerosols Study
and Human Health Risk Assessment

LTC MARK A. MELANSON, Ph.D., CHP
Program Manager, Health Physics
US Army Center for Health Promotion and Preventive Medicine

Slide adapted from: Melanson MA. Depleted Uranium CAPSTONE Aerosols Study and Human Health Risk Assessment. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Apr 7, 2005; Washington, DC.

Military Unique Exposures

- For over 30 years, the DoD has evaluated the safety of DU munitions and armor with this most recent assessment in 2004
- U.S. used DU for the first time in combat during Operation Desert Storm in 1991
- Fratricide ("friendly fire") involving six Abrams tanks and fourteen Bradley Fighting Vehicles in 1991
- As reported in the USACHPPM 2000 Report, existing data were not robust enough for modeling doses to personnel inside Abrams and Bradleys perforated by DU munitions

Slide adapted from: Melanson MA. Depleted Uranium CAPSTONE Aerosols Study and Human Health Risk Assessment. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Apr 7, 2005; Washington, DC.

DU CAPSTONE Aerosol Study and Human Health Risk Assessment

- $ 6 Million Project
- 5 years to complete
- Rigorous science
- External Peer Review
- Transparent process
- Unlimited release of data

Slide adapted from: Melanson MA. Depleted Uranium CAPSTONE Aerosols Study and Human Health Risk Assessment. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Apr 7, 2005; Washington, DC.

Estimating Depleted Uranium Aerosol Doses and Risks:

An Overview of the Capstone Depleted Uranium Aerosol Study

and the Capstone Human Health Risk Assessment

Research Advisory Committee on Gulf War Veterans' Illnesses
April 7, 2005

Mary Ann Parkhurst
Battelle/Pacific Northwest National Laboratory
Richland, Washington

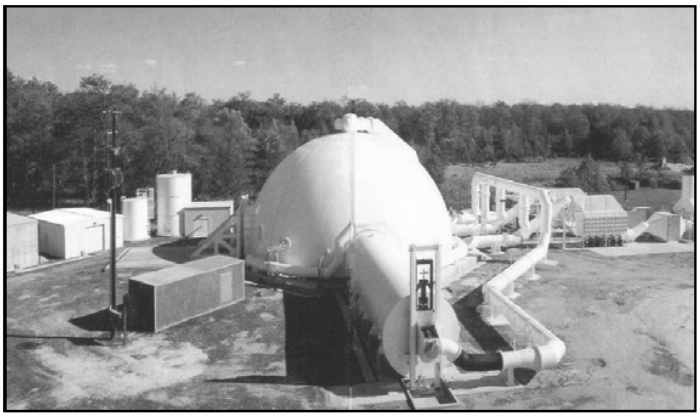
Slide adapted from: Parkhurst MA. Estimating Depleted Uranium Aerosol Doses and Risks: An Overview of the Capstone Depleted Uranium Study and the Capstone Human Health Risk Assessment. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Apr 7, 2005; Washington, DC.

Capstone DU Aerosol Study

- Large-scale field testing of aerosols generated by perforation of armored vehicles with depleted uranium (DU) penetrators
- Highest priority on aerosols created inside vehicle at time of and immediately after perforation
- Fired at ballistic turrets and hulls
- Collected aerosol and deposited particulate material
- Characterized chemical composition and particle size collected over first 2 hours

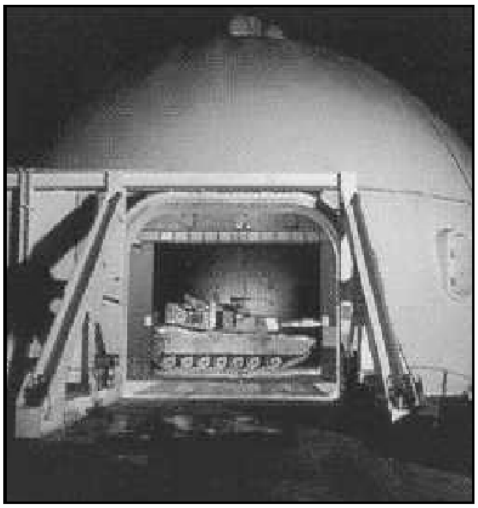
Slide adapted from: Parkhurst MA. Estimating Depleted Uranium Aerosol Doses and Risks: An Overview of the Capstone Depleted Uranium Study and the Capstone Human Health Risk Assessment. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Apr 7, 2005; Washington, DC.

ATC SUPERBOX FACILITY



Slide adapted from: Parkhurst MA. Estimating Depleted Uranium Aerosol Doses and Risks: An Overview of the Capstone Depleted Uranium Study and the Capstone Human Health Risk Assessment. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Apr 7, 2005; Washington, DC.

ATC SUPERBOX SHOT



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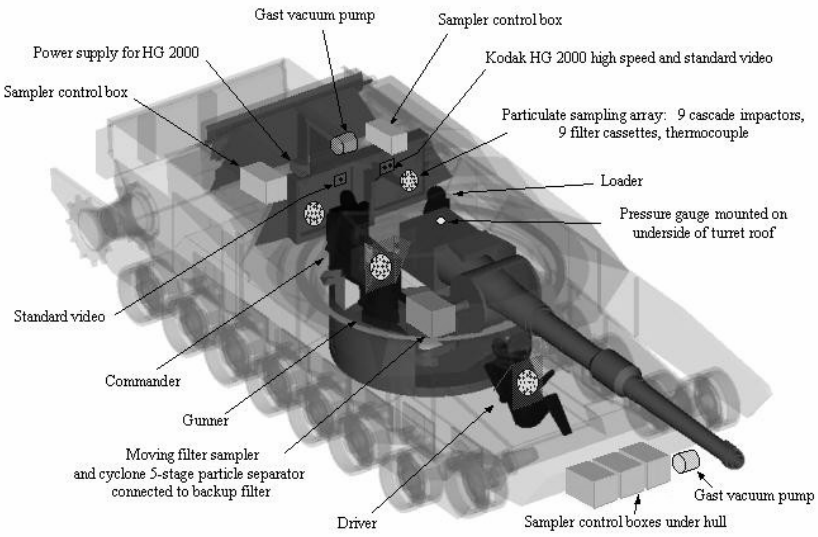

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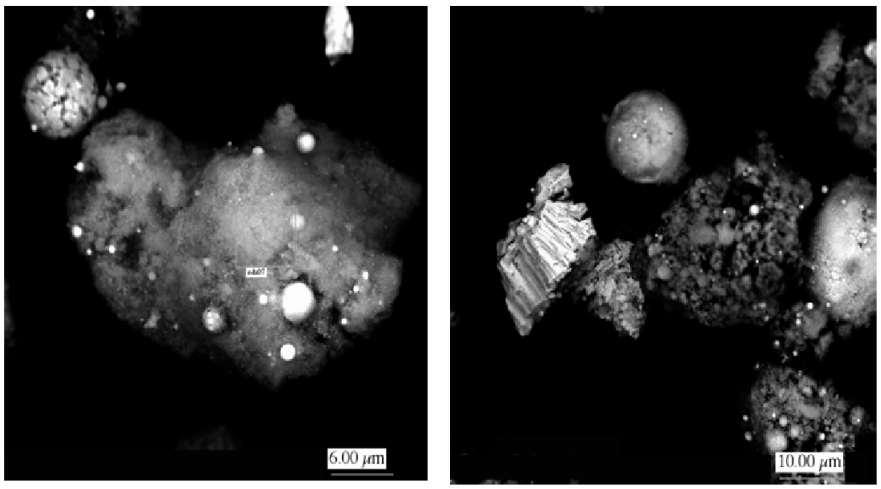
DU Aerosol Analysis

- 8,000 samples collected
- Analysis performed by 4 laboratories

Slide adapted from: Parkhurst MA. Estimating Depleted Uranium Aerosol Doses and Risks: An Overview of the Capstone Depleted Uranium Study and the Capstone Human Health Risk Assessment. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Apr 7, 2005; Washington, DC.

Less Dense Aggregates



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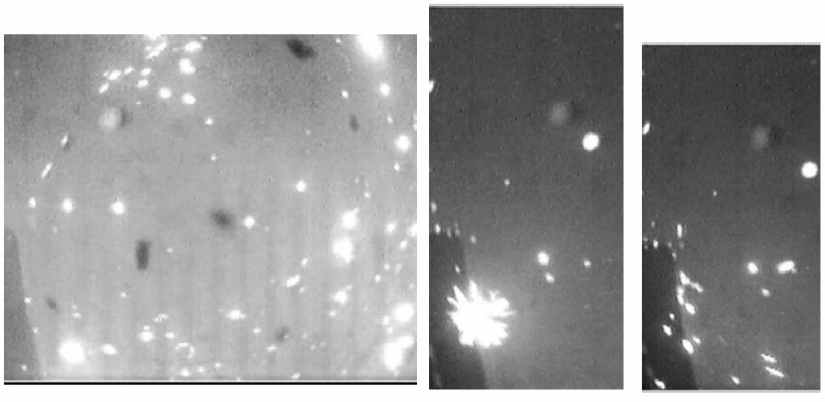
Transient Fireflies



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Median 50-yr Committed Effective Doses

Scenarios	E(50), rem			
	Abrams Tank: Conventional Armor, No Ventilation	Abrams Tank: DU Armor, No Ventilation	Abrams Tank: DU Armor, EC/NBC Operating	Bradley Vehicle: Conventional Armor, No Ventilation
Most Likely				
A - Crew, exit in 1 min	2.0	2.2	0.090	0.59
B - Crew, exit in 5 min	3.7	6.0	0.44	1.7
E - First responders	0.92	1.9	0.41	0.89
Upper Bound				
C - Crew, exit in 1 h	4.8	8.3	1.02	2.1
D - Crew, exit in 2 h	5.0	8.7	1.20	2.4

Slide adapted from: Parkhurst MA. Estimating Depleted Uranium Aerosol Doses and Risks: An Overview of the Capstone Depleted Uranium Study and the Capstone Human Health Risk Assessment. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Apr 7, 2005; Washington, DC.

Median Lifetime Risk Increase of Fatal Cancer from DU Inhalation

Scenario	Lifetime Risk Increase of Fatal Cancer (%)			
	Abrams Tank: Conventional Armor, No Ventilation	Abrams Tank: DU Armor, No Ventilation	Abrams Tank: DU Armor, EC/NBC Operating	Bradley Vehicle: Conventional Armor, No Ventilation
Most Likely				
A – Crew, exit in 1 min	0.11	0.12	0.0049	0.034
B – Crew, exit in 5 min	0.20	0.32	0.025	0.099
E – First responders	0.050	0.10	0.023	0.052
Upper Bound				
C – Crew, Exit in 1 h	0.27	0.44	0.057	0.12
D – Crew, Exit in 2 h	0.28	0.45	0.065	0.14

Slide adapted from: Parkhurst MA. Estimating Depleted Uranium Aerosol Doses and Risks: An Overview of the Capstone Depleted Uranium Study and the Capstone Human Health Risk Assessment. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Apr 7, 2005; Washington, DC.

The Bottom Line—Radiological Effects

- For all vehicle configurations and modeled exposure times, except for the *unventilated* Abrams tank perforated through DU armor, predicted radiation doses were within U.S. (routine) occupational limits.
- For the *unventilated* Abrams tank perforated through DU armor, short exposures (about 1 min) were within routine occupational limits, and exposures up to 2 h were within the emergency or planned special exposure limits.
- *For all vehicle configurations and exposure times modeled (up to 2 h), predicted radiation doses are not likely to cause adverse health effects*.

Slide adapted from: Parkhurst MA. Estimating Depleted Uranium Aerosol Doses and Risks: An Overview of the Capstone Depleted Uranium Study and the Capstone Human Health Risk Assessment. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Apr 7, 2005; Washington, DC.

The Bottom Line—Toxicological Effects

- In the case of the *unventilated* Abrams tank perforated through conventional armor, the potential exists for short-term adverse kidney effects for exposures 5 min or longer.
- In all other cases, *predicted uranium concentrations in the kidney are not likely to cause adverse chemically-induced health effects*.

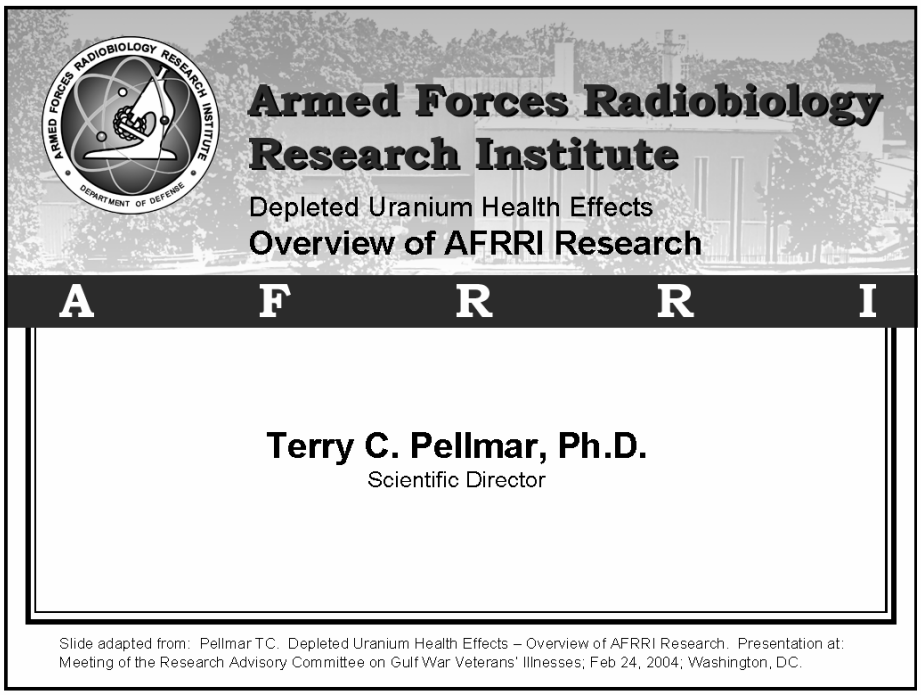
Slide adapted from: Parkhurst MA. Estimating Depleted Uranium Aerosol Doses and Risks: An Overview of the Capstone Depleted Uranium Study and the Capstone Human Health Risk Assessment. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Apr 7, 2005; Washington, DC.

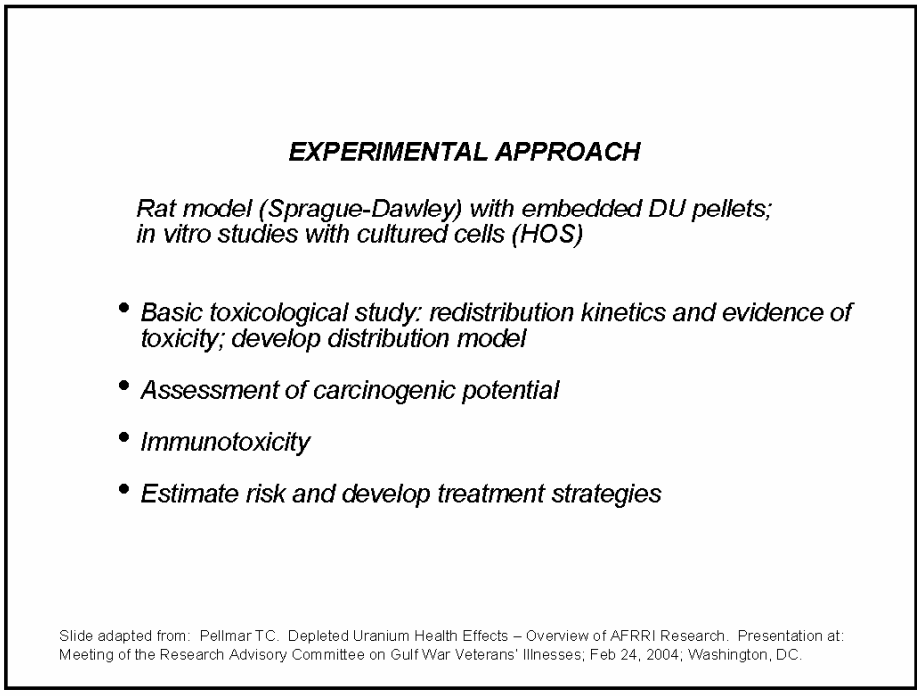
Slide adapted from: Parkhurst MA. Estimating Depleted Uranium Aerosol Doses and Risks: An Overview of the Capstone Depleted Uranium Study and the Capstone Human Health Risk Assessment. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Apr 7, 2005; Washington, DC.

Animal Studies: Effects of DU exposures via different routes, on different biological systems

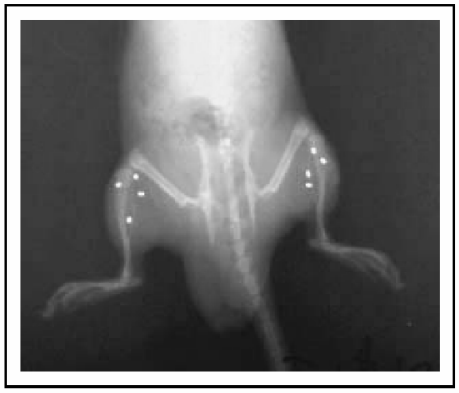
Depleted Uranium

★☆★ RAC-GWVI


Armed Forces Radiobiology Research Institute
Depleted Uranium Health Effects
Overview of AFRRI Research
A F R R I
Terry C. Pellmar, Ph.D.
Scientific Director
Slide adapted from: Pellmar TC. Depleted Uranium Health Effects – Overview of AFRRI Research. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Feb 24, 2004; Washington, DC.


EXPERIMENTAL APPROACH
Rat model (Sprague-Dawley) with embedded DU pellets; in vitro studies with cultured cells (HOS)
• Basic toxicological study: redistribution kinetics and evidence of toxicity; develop distribution model
• Assessment of carcinogenic potential
• Immunotoxicity
• Estimate risk and develop treatment strategies
Slide adapted from: Pellmar TC. Depleted Uranium Health Effects – Overview of AFRRI Research. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Feb 24, 2004; Washington, DC.

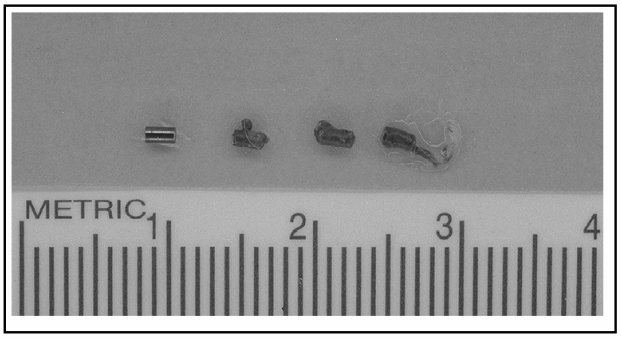
Implanted DU pellets



Slide adapted from: Pellmar TC. Depleted Uranium Health Effects – Overview of AFRRI Research. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Feb 24, 2004; Washington, DC.

DU Distribution and Toxicity...

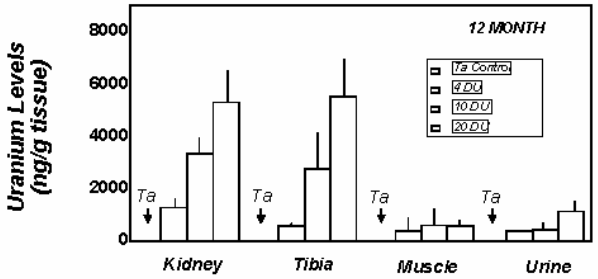
DU pellet implants: new and 90 days



Slide adapted from: Pellmar TC. Depleted Uranium Health Effects – Overview of AFRRI Research. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Feb 24, 2004; Washington, DC.

DU Distribution and Toxicity...

Uranium Distribution in Rat Tissue after DU Pellet Implantation



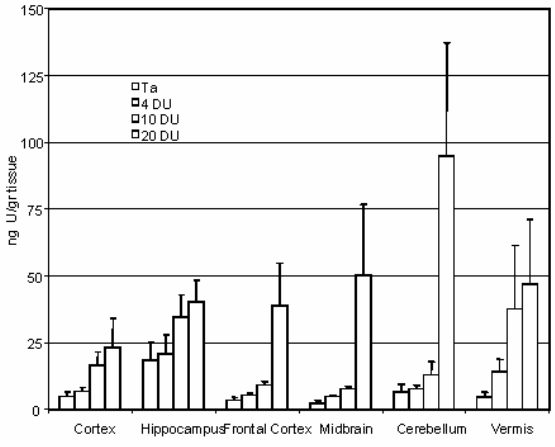
- ***Uranium redistributes with time to various organs and tissues, especially bone and kidney. Uranium also distributes to brain, lymph nodes, and testes.***
- ***No apparent changes in kidney or bone histology***

Pellmar et al., Toxicol. Sci. 49, 29-39 (1999)

Slide adapted from: Pellmar TC. Depleted Uranium Health Effects – Overview of AFRRI Research. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Feb 24, 2004; Washington, DC.

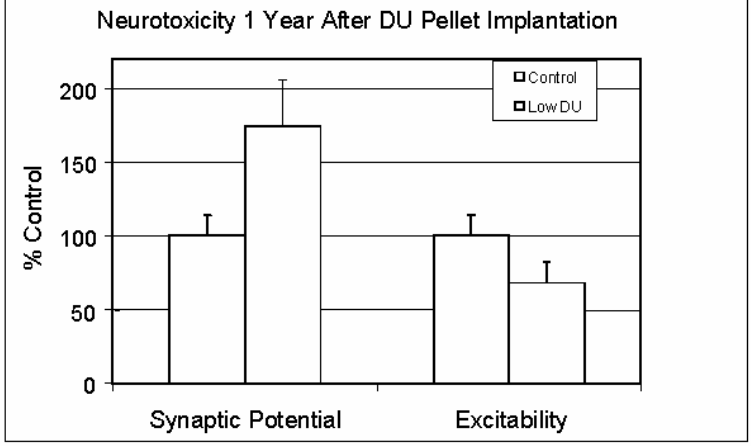
DU Distribution and Toxicity...

- ***Non-homogeneous distribution of uranium in the brain***



Pellmar et al., Neurotoxicol. 20, 785-792 (1999)

Slide adapted from: Pellmar TC. Depleted Uranium Health Effects – Overview of AFRRI Research. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Feb 24, 2004; Washington, DC.



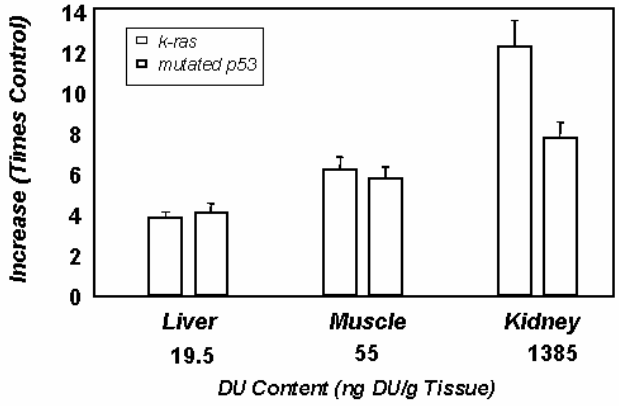
- *DU altered electrophysiological activity in the hippocampus*
- *No gross behavioral changes were observed*

Pellmar et al., Neurotoxicol. 20, 785-792 (1999)

Slide adapted from: Pellmar TC. Depleted Uranium Health Effects – Overview of AFRRI Research. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Feb 24, 2004; Washington, DC.

Transformation, Mutagenicity, Carcinogenicity...

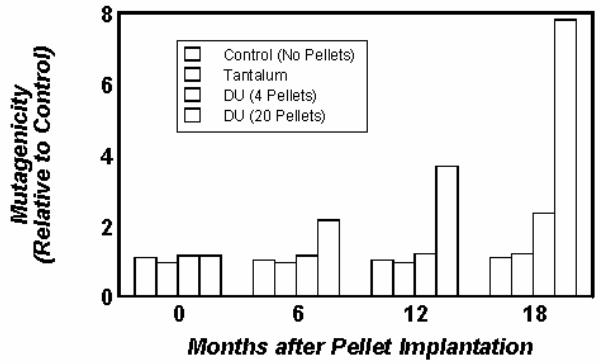
Increased Oncogenes



- *DU induces oncogenes known to be involved in carcinogenesis*

Slide adapted from: Pellmar TC. Depleted Uranium Health Effects – Overview of AFRRI Research. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Feb 24, 2004; Washington, DC.

Transformation, Mutagenicity, Carcinogenicity...



- *Urine from DU animals is mutagenic*

Miller et al., Mutagenesis, 13, 643-648 (1998)

Slide adapted from: Pellmar TC. Depleted Uranium Health Effects – Overview of AFRRI Research. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Feb 24, 2004; Washington, DC.

Transformation, Mutagenicity, Carcinogenicity...

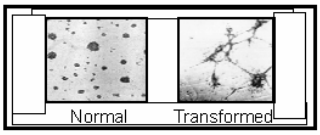
- *DU and tungsten alloy metals induce genetic changes to extent similar to known carcinogens beryllium and nickel*

	DU (Soluble)	DU (Insoluble)	WNiCo*	Be	Ni
Micronuclei Induction	↑	↑	↑	↑	↑
Sister Chromatid Exchange	↑	↑	↑	↑	↑
DNA Single-Strand Breaks	↑	↑	↑	(not done)	↑
Dicentric Formation	↑	↑	(not done)	(not done)	No Change

*WNiCo: reconstituted metal mixture of tungsten (W), nickel (Ni), and cobalt (Co) typical of tungsten military alloy

Slide adapted from: Pellmar TC. Depleted Uranium Health Effects – Overview of AFRRI Research. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Feb 24, 2004; Washington, DC.

Transformation, Mutagenicity, Carcinogenicity...



Normal and DU-Transformed HOS Cells

	Untreated	Tungsten	Tungsten/Nickel Cobalt	Nickel	Lead	Soluble DU	Insoluble DU	DU/Phenyl Acetate
Transformation Rate*	4.2	28.2	121.5	29.9	21.1	40.2	115.9	4.7
Tumorigenicity**	0 (0/82)	.33 (8/24)	.83 (10/12)	.29 (7/24)	.10 (2/20)	.44 (11/25)	.65 (13/20)	0 (0/12)

** Number of transformed cells per 500,000 surviving cells*
***Number of tumors formed when 1 million transformed cells injected into immune compromised mice*

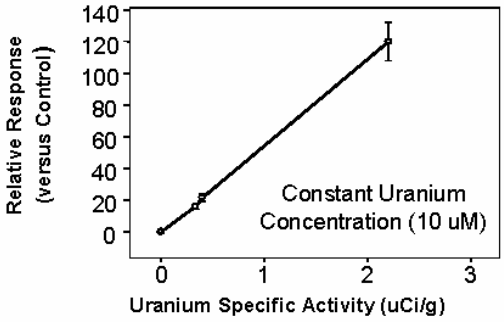
- ***DU transforms cells to a tumorigenic phenotype; cells form tumors in mice***

Miller et al., Environ. Health Persp. 106, 465-471 (1998); Miller et al., Radiat. Res. (In Press)

Slide adapted from: Pellmar TC. Depleted Uranium Health Effects – Overview of AFRRI Research. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Feb 24, 2004; Washington, DC.

Transformation, Mutagenicity, Carcinogenicity...

Radiation vs. Chemical Toxicity of DU
Neoplastic Transformation Assay



- ***DU-induced transformation rate is influenced by radioactivity of DU, not just chemical toxicity***

Miller et al.,Radiation Protection Dosimetry, submitted

Slide adapted from: Pellmar TC. Depleted Uranium Health Effects – Overview of AFRRI Research. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Feb 24, 2004; Washington, DC.

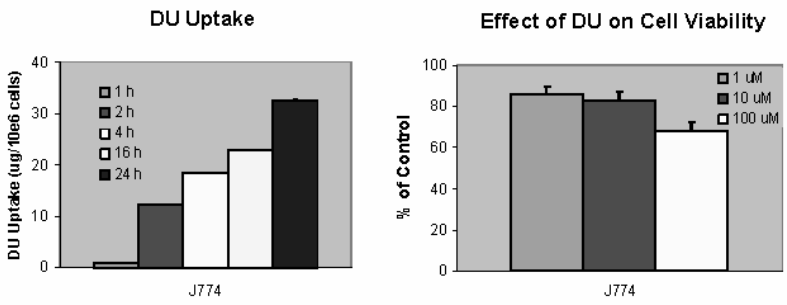
Immunotoxicity

Principal Investigators: David McClain, Ph.D. and John Kalinich, Ph.D.

- *Immune system is represented in a variety of tissues*
- *Other heavy metals have been shown to be immunotoxic*
- *AFRRI DU Distribution and Toxicity study determined there are alterations in several immune system parameters in DU-implanted rats*

Slide adapted from: Pellmar TC. Depleted Uranium Health Effects – Overview of AFRRI Research. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Feb 24, 2004; Washington, DC.

Immunotoxicity



- ***Soluble DU is taken up and concentrated by cultured macrophages, affecting their metabolic viability, and eventually leading to their death***

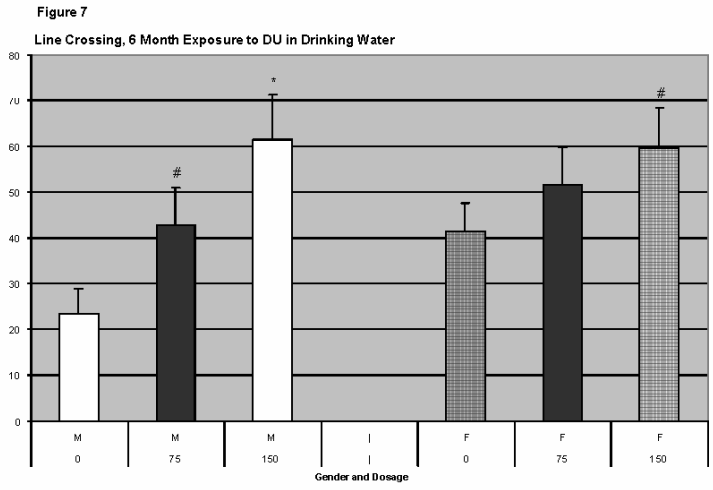
Slide adapted from: Pellmar TC. Depleted Uranium Health Effects – Overview of AFRRI Research. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Feb 24, 2004; Washington, DC.

Behavioral Changes and Brain Lipid Oxidation Following Uranium Exposure

Wayne Briner
Jennifer Murray

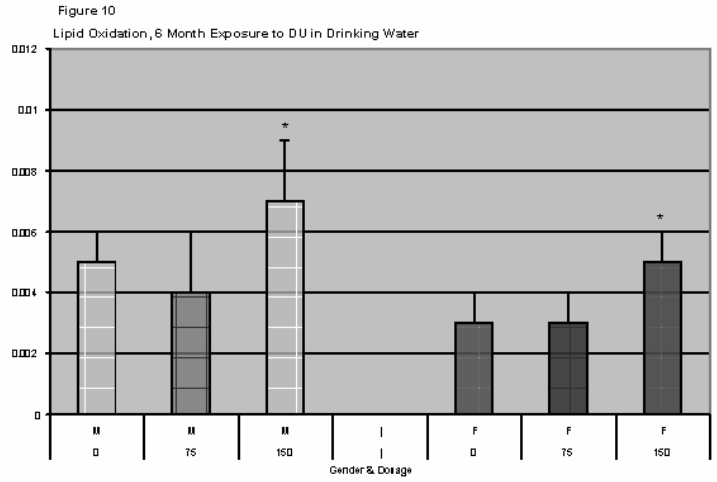
University of Nebraska Kearney

Line Crossing, 6 months



Slide adapted from: Briner W. Behavioral Changes and Brain Lipid Oxidation Following Uranium Exposure. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Apr 7, 2005; Washington, DC.

Lipid Oxidation (adult, 6 months)

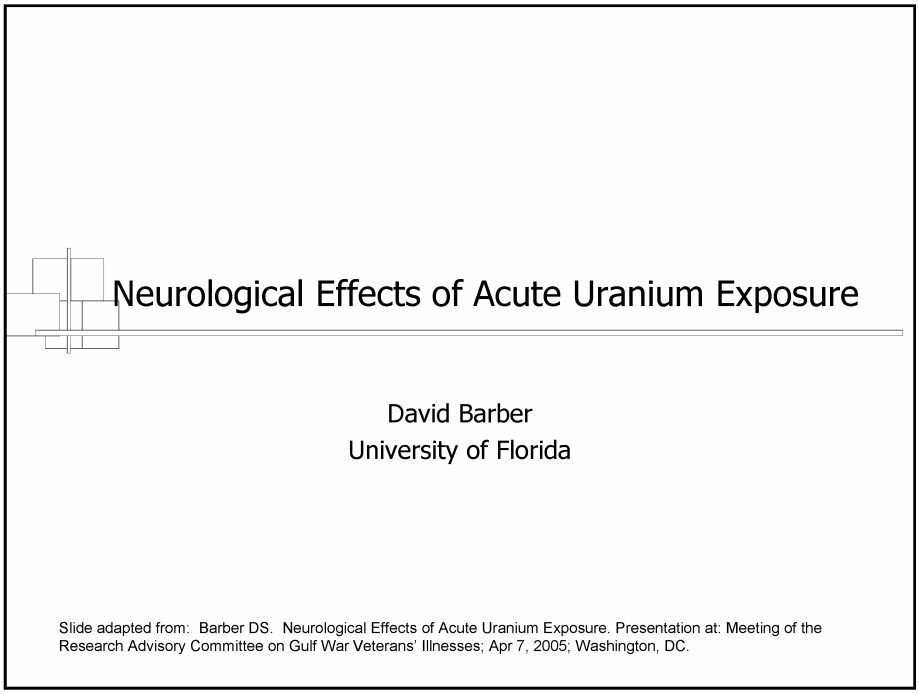


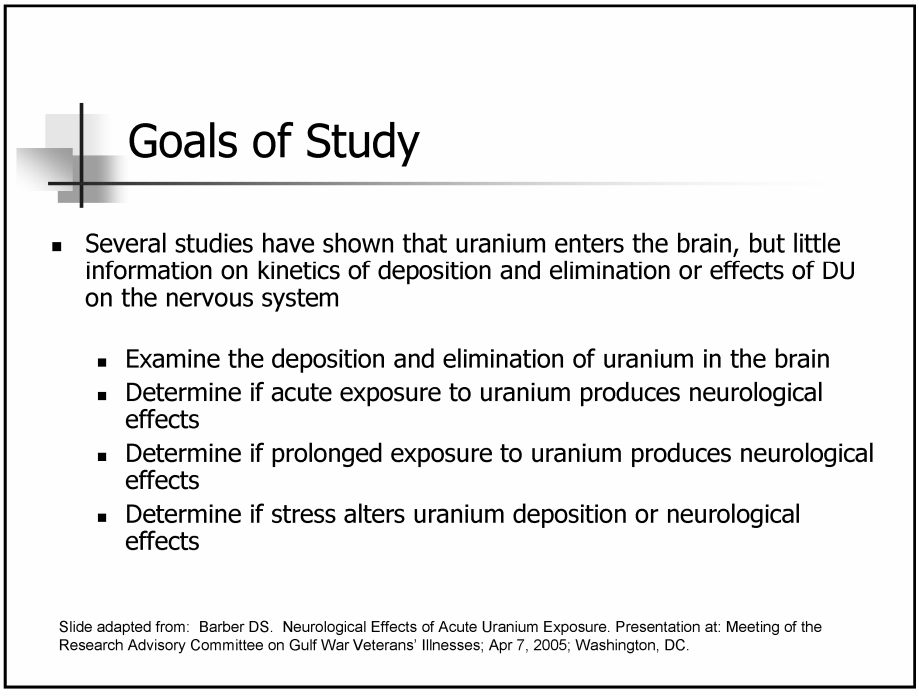
Slide adapted from: Briner W. Behavioral Changes and Brain Lipid Oxidation Following Uranium Exposure. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Apr 7, 2005; Washington, DC.

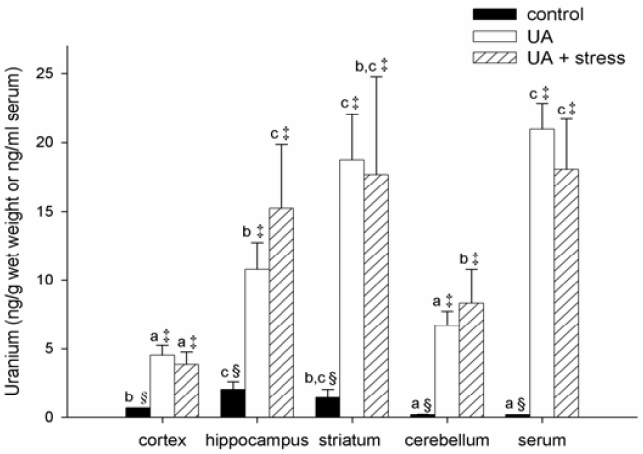
Overview

- Behavioral changes in adults and developing animals
- Changes seen in two species
- Produces lipid oxidation in CNS (direct/indirect?)
- Lipid oxidation related to behavioral alterations
- Complex effects on midbrain neurotransmitter profile

Slide adapted from: Briner W. Behavioral Changes and Brain Lipid Oxidation Following Uranium Exposure. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Apr 7, 2005; Washington, DC.


Neurological Effects of Acute Uranium Exposure
David Barber
University of Florida
Slide adapted from: Barber DS. Neurological Effects of Acute Uranium Exposure. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Apr 7, 2005; Washington, DC.


Goals of Study
Several studies have shown that uranium enters the brain, but little information on kinetics of deposition and elimination or effects of DU on the nervous system
Examine the deposition and elimination of uranium in the brain
Determine if acute exposure to uranium produces neurological effects
Determine if prolonged exposure to uranium produces neurological effects
Determine if stress alters uranium deposition or neurological effects
Slide adapted from: Barber DS. Neurological Effects of Acute Uranium Exposure. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Apr 7, 2005; Washington, DC.



Barber et al., 2005

Slide adapted from: Barber DS. Neurological Effects of Acute Uranium Exposure. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Apr 7, 2005; Washington, DC.

- This study demonstrated that:
  - There are regional differences in brain uranium distribution
  - There are several phases of uranium elimination from the brain with the last phase being very long
  - Prior stress did not exacerbate the entry of uranium into the brain, if anything increased its elimination

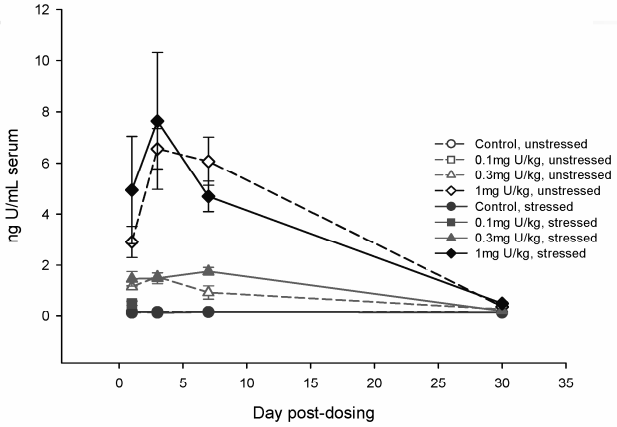
Slide adapted from: Barber DS. Neurological Effects of Acute Uranium Exposure. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Apr 7, 2005; Washington, DC.

Experimental Design

- Male Sprague Dawley rats
- Stress applied for 5 days prior to uranium exposure (restraint + swim)
- 0, 0.1, 0.3, and 1.0 mg uranium/kg administered as uranyl acetate by i.m. injection
- Tissue samples taken at 1, 3, 7,and 30 days for uranium levels, neurotransmitters, GSH, receptor number, and histopathology
  - Rats perfused with cold saline
  - Cerebral cortex, hippocampus, striatum, hypothalamus and cerebellum removed
  - Whole body perfusion fixation for histopathology

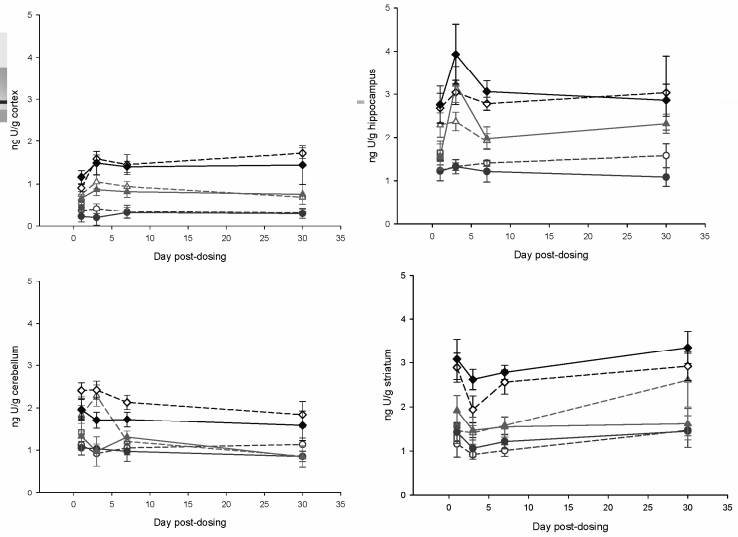
Slide adapted from: Barber DS. Neurological Effects of Acute Uranium Exposure. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Apr 7, 2005; Washington, DC.

Serum uranium



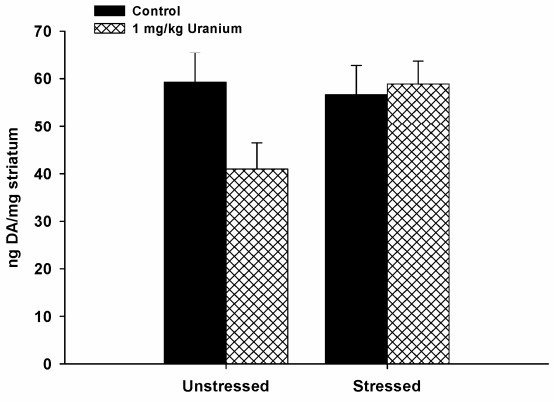
Slide adapted from: Barber DS. Neurological Effects of Acute Uranium Exposure. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Apr 7, 2005; Washington, DC.

Brain Uranium



Slide adapted from: Barber DS. Neurological Effects of Acute Uranium Exposure. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Apr 7, 2005; Washington, DC.

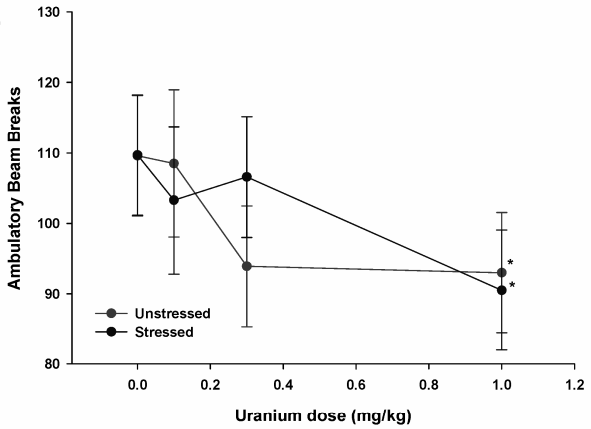
Striatal Dopamine on PD 3



Uranium exposure decreases striatal dopamine in unstressed rats. Values are mean ± SD (N=5). * indicates values that are significantly different from control ($p<0.05$).

Slide adapted from: Barber DS. Neurological Effects of Acute Uranium Exposure. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Apr 7, 2005; Washington, DC.

Ambulatory activity on PD 27



Slide adapted from: Barber DS. Neurological Effects of Acute Uranium Exposure. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Apr 7, 2005; Washington, DC.

Uranium exposure decreases forelimb grip strength

Day post-dosing	Uranium dose (mg/kg)	Forelimb Grip Strength (kg)	
		Unstressed	Stressed
6	0	1.83 ± 0.04	1.81 ± 0.05
	0.1	1.87 ± 0.04	1.79 ± 0.05
	0.3	1.79 ± 0.03	1.76 ± 0.03
	1.0	**1.70 ± 0.07**	1.79 ± 0.04
13	0	1.96 ± 0.04	1.94 ± 0.04
	0.1	2.01 ± 0.02	2.05 ± 0.03
	0.3	1.91 ± 0.04	1.96 ± 0.04
	1.0	**1.86 ± 0.04**	1.93 ± 0.03
20	0	2.01 ± 0.06	1.98 ± 0.05
	0.1	1.98 ± 0.07	2.06 ± 0.04
	0.3	1.90 ± 0.04	1.94 ± 0.05
	1.0	**1.87 ± 0.06**	1.96 ± 0.04
27	0	2.06 ± 0.06	2.08 ± 0.05
	0.1	2.08 ± 0.03	2.09 ± 0.07
	0.3	1.99 ± 0.04	2.10 ± 0.04
	1.0	**1.91 ± 0.05**	1.99 ± 0.04

Slide adapted from: Barber DS. Neurological Effects of Acute Uranium Exposure. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Apr 7, 2005; Washington, DC.

Summary

- A single intramuscular injection of uranyl acetate increased brain uranium for at least 30 days. Hippocampus and striatum accumulated higher uranium levels than cortex and cerebellum.
- A single exposure to uranyl acetate is capable of producing neurological effects that last for at least 27 days after exposure
- Stress at the time of uranium exposure had little effect on uranium levels, but did alter some behavioral and neurochemical parameters
  - Dose dependent decreases in ambulatory activity were observed. These effects were not significantly altered by prior stress.
  - A transient decrease in striatal dopamine was observed. This was ameliorated by prior stress
  - Small dose dependent decreases in forelimb grip strength were observed. These were ameliorated by prior stress.

Slide adapted from: Barber DS. Neurological Effects of Acute Uranium Exposure. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Apr 7, 2005; Washington, DC.

- All doses produced some degree of uremia. It is difficult to separate direct neurological effects of uranium from secondary effects due to uremia.
- The timing, duration, and effect of stress suggest that effect on dopamine and forelimb grip strength may be direct effects of uranium.

Slide adapted from: Barber DS. Neurological Effects of Acute Uranium Exposure. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Apr 7, 2005; Washington, DC.

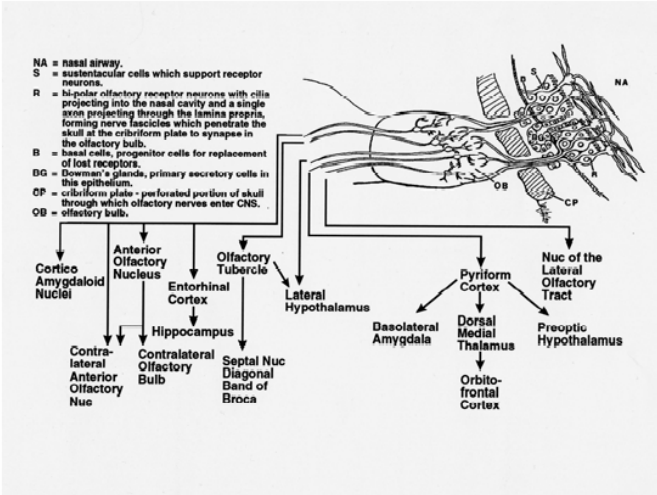
Inhalation of Uranium Oxides to Mimic Gulf War Exposures: Deposition and toxicity in brain, lung, and kidney

Johnnye Lewis, Ph.D., DABT
Director, Community Environmental Health Program, University of New Mexico Health Sciences Center

Co-Investigators:
Graham Bench, Ph.D., CAMS, Lawrence Livermore National Laboratory
Fletcher Hahn, DVM, Ph.D., DACVP, Lovelace Respiratory Research Institute
Jenny Karlsson, Ph.D., Community Environmental Health Program, UNM HSC
Ed Barr, MSEE, Lovelace Respiratory Research Institute

Slide adapted from: Lewis J. Inhalation of Uranium Oxides to Mimic Gulf War Exposures: Deposition and toxicity in brain, lung, and kidney. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; February 24, 2004; Washington, DC.

Nose-Brain Barrier



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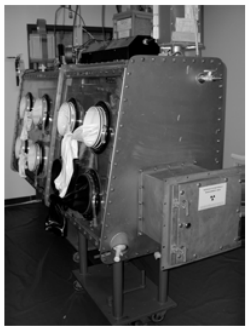
DU as a contributor

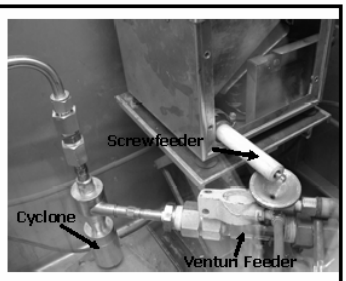
- **Potential for exposures to DU aerosols**
  - **Tank-Impact – High concentration, acute (15 min) exposure**
  - **March-Through – Low concentration – single day**
  - **Clean-up – Low concentration – up to 30 day**
  - **Maintenance – Very low concentration – longer duration**
- **Aerosols resulted from impact, combustion, resuspension**
  - **Estimates of exposure inconsistent**
    - **Varied from 300 micrograms to >25 grams**
    - **Estimates of solubility and respirability varied**
  - **Respirable fraction could move suspended for hours**
- **Other heavy metals neurotoxic and neuroimmunotoxic**

Slide adapted from: Lewis J. Inhalation of Uranium Oxides to Mimic Gulf War Exposures: Deposition and toxicity in brain, lung, and kidney. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; February 24, 2004; Washington, DC.

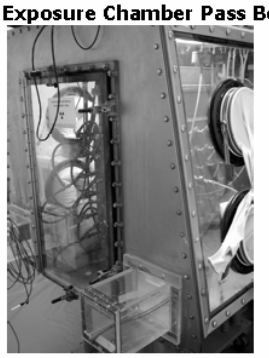
Glove Box Enclosure System



Aerosol Generation System



Exposure Chamber Pass Box



96-Port Nose-Only Exposure Chamber

EXPOSURE

Ed Barr, MSEE

Lovelace Respiratory Research Institute

Slide adapted from: Lewis J. Inhalation of Uranium Oxides to Mimic Gulf War Exposures: Deposition and toxicity in brain, lung, and kidney. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; February 24, 2004; Washington, DC.

Pathology at 4 hr post-exposure

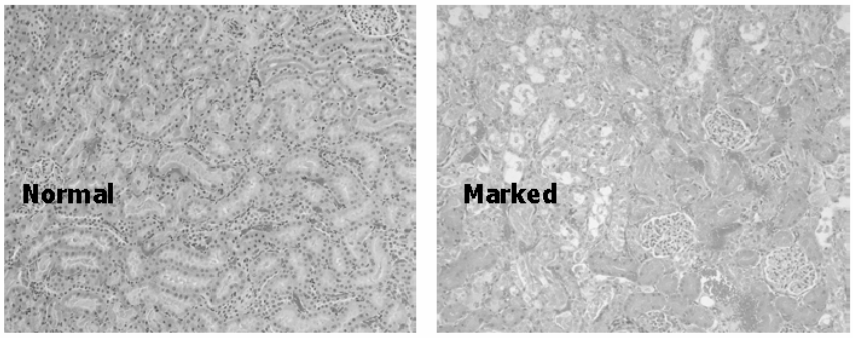
Tank-Impact Scenario

(Moribund sacs & deaths at <14 d included)

Slide adapted from: Lewis J. Inhalation of Uranium Oxides to Mimic Gulf War Exposures: Deposition and toxicity in brain, lung, and kidney. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; February 24, 2004; Washington, DC.

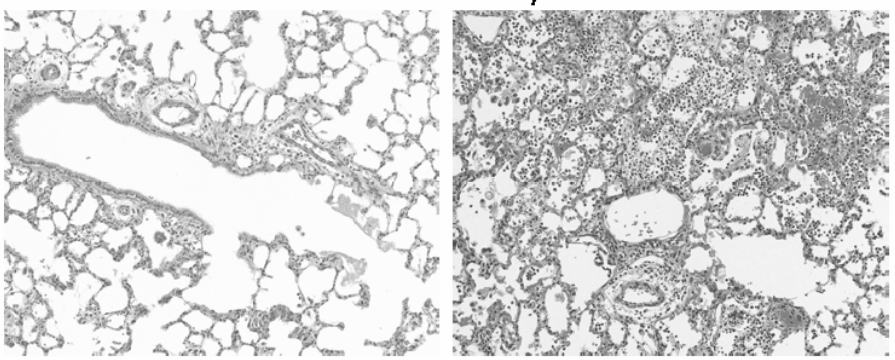
Renal Tubular Necrosis

More soluble UO_3 resulted in renal tubular necrosis and uremia



Slide adapted from: Lewis J. Inhalation of Uranium Oxides to Mimic Gulf War Exposures: Deposition and toxicity in brain, lung, and kidney. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; February 24, 2004; Washington, DC.

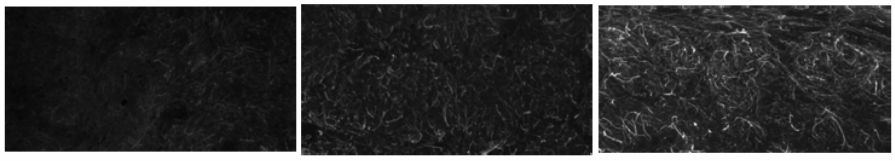
Uremic Pneumonia
Mild vs. Marked, Fatal



- **Uremic pneumonia was the immediate cause of death**
- **Females had a higher death rate**

Slide adapted from: Lewis J. Inhalation of Uranium Oxides to Mimic Gulf War Exposures: Deposition and toxicity in brain, lung, and kidney. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; February 24, 2004; Washington, DC.

GFAP 4 hours post 15 min high dose exposure *Tank-impact Scenario*



Control DUOx UO3

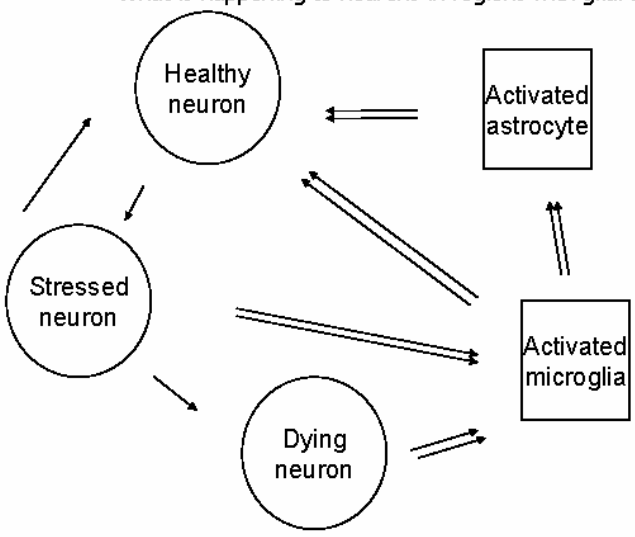
Slide adapted from: Lewis J. Inhalation of Uranium Oxides to Mimic Gulf War Exposures: Deposition and toxicity in brain, lung, and kidney. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; February 24, 2004; Washington, DC.

Brain inflammation – GFAP data
Tank-impact scenario

- **Solubility related increase in GFAP**
- **Females appear to show greater response**
- **Time x gender x exposure interaction**
- **Endotoxin increases GFAP response in all exposures**
  - **Females show greater increase with U exposure**

Slide adapted from: Lewis J. Inhalation of Uranium Oxides to Mimic Gulf War Exposures: Deposition and toxicity in brain, lung, and kidney. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; February 24, 2004; Washington, DC.

What is happening to neurons in regions with glial activation?



Slide adapted from: Lewis J. Inhalation of Uranium Oxides to Mimic Gulf War Exposures: Deposition and toxicity in brain, lung, and kidney. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; February 24, 2004; Washington, DC.

Conclusions

- **Very Short/High Dose – *Tank-Impact* scenario**
  - **no detectable CNS uptake regardless of solubility**
  - **Solubility-related neuroinflammation**
  - **Most soluble forms result in extensive renal deposition and renal toxicity**
  - **Females more sensitive to CNS & renal toxicity**
- **Short-term/ Moderate Dose – *March-Through* Scenario**
  - **Nasal inflammation increases the probability of CNS deposition and transport with low dose inhalation for 6 hr durations**
- **Longer-duration/ Moderate Dose – *Clean-Up* Scenario**
  - **No uptake observable in animals without inflammation**

Slide adapted from: Lewis J. Inhalation of Uranium Oxides to Mimic Gulf War Exposures: Deposition and toxicity in brain, lung, and kidney. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; February 24, 2004; Washington, DC.

Epidemiologic Studies: Associations between DU exposure and health outcomes in Gulf War veterans

Depleted Uranium

★☆★ RAC-GWVI

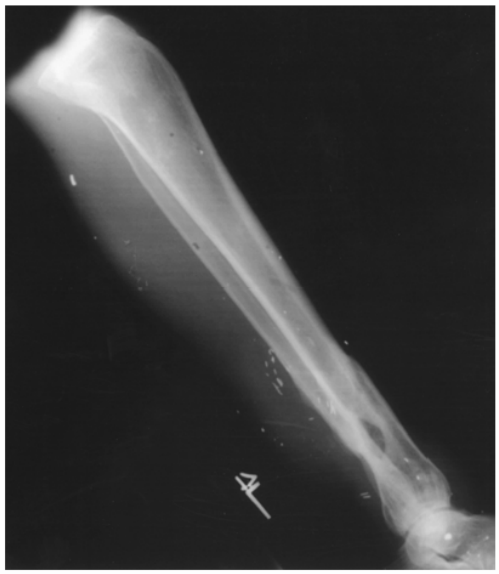
Epidemiologic Studies: Association of DU With GWI-related Health Outcomes

Study	Exposure	Outcome	OR
Haley, 1997 (249 Seabeas)	s/r DU exposure	any of 3 defined syndromes	ns
Spencer, 2001 (241 GWI cases, 113 controls)	s/r DU exposure	GWI case CMI case	OR = 3.69 (1.54 – 8.81) OR = 4.46 (1.74 – 11.40)
Suadicini, 1999 (686 Danish Gulf War vets)	s/r DU exposure	3+ neuro-psych symptoms	OR = 2.3 (0.95-5.7)
Australian study (1,456 Australian vets)	s/r contact with DU shell casings	functional impairment in prior 2 weeks	OR = 1.1 (0.8-1.6)

HEALTH EFFECTS OF DEPLETED URANIUM IN EXPOSED GULF WAR VETERANS – A TEN-YEAR FOLLOW-UP

Melissa A. McDiarmid, M.D., M.P.H.
VA Maryland Health Care System
Baltimore Division

Slide adapted from: McDiarmid MA. Health Effects of Depleted Uranium in Exposed Gulf War Veterans – A Ten-Year Follow-Up. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; February 24, 2004; Washington, DC.



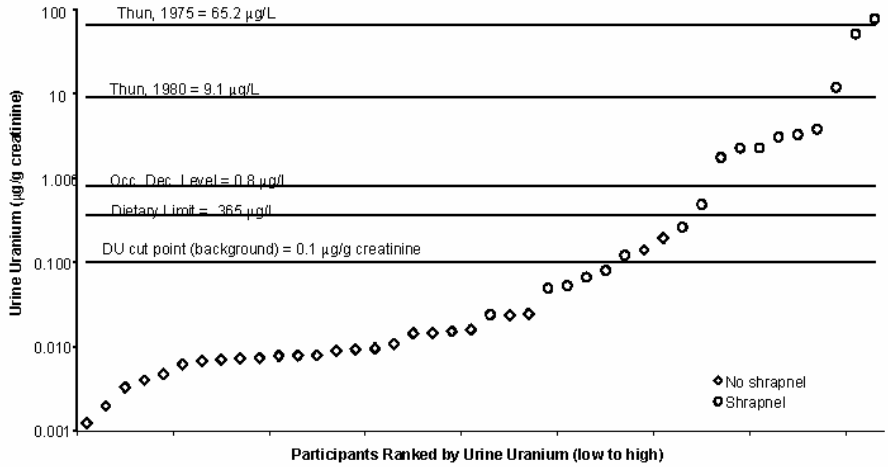
Slide adapted from: McDiarmid MA. Health Effects of Depleted Uranium in Exposed Gulf War Veterans – A Ten-Year Follow-Up. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; February 24, 2004; Washington, DC.

Summary of Surveillance Visits

Year	Cases	Non-exposed	Total
1993-4	33		33
1997	29	38	67
1999	21+29 new		50
2001	31+8 new (17 original cases)		39
2003	32		32

A total of 70 individuals involved in friendly fire incidents have been evaluated at Baltimore.

Slide adapted from: McDiarmid MA. Health Effects of Depleted Uranium in Exposed Gulf War Veterans – A Ten-Year Follow-Up. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; February 24, 2004; Washington, DC.



Slide adapted from: McDiarmid MA. Health Effects of Depleted Uranium in Exposed Gulf War Veterans – A Ten-Year Follow-Up. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; February 24, 2004; Washington, DC.

Hematologic Parameters Summary (2001)

Laboratory test (normal range)	Low Uranium Group[a] (mean ± SE)	High Uranium Group[b] (mean ± SE)	Mann - Whitney Test (p)
White Blood Cells (4.8-10.8 K/cm^2)	6.53 ± 0.41	5.85 ± 0.45	0.36
Hematocrit (4252%)	**44.60 ± 0.43**	**42.59 ± 0.80**	**0.03**
Hemoglobin (1418 g/dL)	**15.40 ± 0.15**	**14.79 ± 0.32**	**0.07**
Platelets (140-440 K/cm^2)	254.54 ±13.82	234.08 ± 13.73	0.21
Lymphocytes (%) (15-45%)	36.87 ± 1.99	36.07 ± 1.81	0.80
Neutrophils (%) (40-75%)	50.95 ± 2.09	51.83 ± 1.97	0.74
Basophils (%) (0-2%)	0.78 ± 0.10	0.65 ± 0.07	0.54
Eosinophils (%) (0-4%)	3.60 ± 0.35	3.51 ± 0.44	0.85
Monocytes (%) (2-12%)	7.79 ±0.37	7.94 ± 0.48	0.99

[a] < 0.10 µg/g creatinine (n=26)
[b] ≥ 0.10 µg/g creatinine (n=13)

Slide adapted from: McDiarmid MA. Health Effects of Depleted Uranium in Exposed Gulf War Veterans – A Ten-Year Follow-Up. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; February 24, 2004; Washington, DC.

Renal Function Parameters (2001)

Laboratory test (normal range)	Low Uranium Group[a] (mean ± SE)	High Uranium Group[b] (mean ± SE)	Mann - Whitney Test (p)
Serum creatinine (0.5-1.1 mg/dL)	**0.95 ± 0.03**	**0.85 ± 0.03**	**0.03**
Serum uric acid (3.4–7 mg/dL)	5.94 ± 0.23	5.85 ± 0.51	0.45
Serum calcium (8.4-10.2 mg/dl)	9.17 ± 0.006	9.27 ± 0.137	0.67
Serum PO4 (2.7-4.5 mg.dl)	3.82 ± 0.101	3.82 ± 0.148	0.63
Urine calcium (100-300 mg/24 hr)	183.50 ± 23.8	214.50 ± 26.3	0.35
Urine PO4 (0.4-1.3 g/24 hr)	1.03 ± 0.008	1.15 ± 0.107	0.40

[a] < 0.10 µg/g creatinine (n=26)
[b] ≥ 0.10 µg/g creatinine (n=13)

Slide adapted from: McDiarmid MA. Health Effects of Depleted Uranium in Exposed Gulf War Veterans – A Ten-Year Follow-Up. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; February 24, 2004; Washington, DC.

Neuroendocrine and Thyroid Hormone Parameters (2001)

Laboratory test (normal range)	Low Uranium Group[a] (mean ± SE)	High Uranium Group[b] (mean ± SE)	Mann - Whitney Test (p)
Prolactin (2.1- 17.7 ng/mL)	**18.84 ± 1.60**	**14.70 ± 2.76**	**0.06**
FSH[c] (.9-15 IU/ml)	4.39 ± 0.50	4.51 ± 0.74	0.95
LH[c] (1.5-9.3 mIU/ml)	5.09 ± 0.51	5.13 ± 1.04	0.48
Testosterone (3-10 ng/ml)	5.64 ± 0.49	4.77 ±0.47	0.28
TSH[c] (0.49-4.67 µIU/ml))	1.99 ±0.24	2.28 ± 0.50	0.89
Free thyroxine (0.7-1.85 ng/dL)	**1.66 ± 0.35**	**1.08 ± 0.07**	**0.02**

[a] < 0.10 µg/g creatinine (n=26)
[b] ≥ 0.10 µg/g creatinine (n=13)
[c] FSH, follicle - stimulating hormone; LH, luteinizing hormone; TSH, thyroid-stimulating hormone

Slide adapted from: McDiarmid MA. Health Effects of Depleted Uranium in Exposed Gulf War Veterans – A Ten-Year Follow-Up. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; February 24, 2004; Washington, DC.

Genotoxicity Parameters (2001)

Laboratory test	Low Uranium Group[a] (mean ± SE(n))	High Uranium Group[b] (mean ± SE(n))	Mann - Whitney Test (p)
Mean aberrations/cell	**0.003 ± 0.001 (26)**	**0.01 ± 0.004 (13)**	**0.027**
Mean SCE[c] untreated	5.07 ± 0.32 (25)	4.39 ± 0.37 (13)	0.199
Mean SCE w/Bleomycin 2 µg/ml	5.42 ± 0.32 (23)	5.95 ± 0.71 (11)	0.663
Mean SCE w/Bleomycin 4 µg/ml	6.31 ± 0.60 (20)	5.30 ± 0.42 (11)	0.197
HPRT MF[d]	10.97 ± 0.97 (26)	19.84 ± 4.89 (13)	0.105

[a] < 0.10 µg/g creatinine
[b] ≥ 0.10 µg/g creatinine
[c] SCE, sister chromatid exchange
[d] HPRT MF, hypoxanthine phosphoribosyl transferase mutation frequency

Slide adapted from: McDiarmid MA. Health Effects of Depleted Uranium in Exposed Gulf War Veterans – A Ten-Year Follow-Up. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; February 24, 2004; Washington, DC.

Recent Publication from VA DU Cohort

Biological monitoring and surveillance results of Gulf War I veterans exposed to depleted uranium. McDiarmid et al, *Int Arch Occup Environ Health Aug 2005 [Epub]*

- **Reports on physical exams and lab evaluations of 32 Gulf veterans with embedded DU shrapnel; 5th exam**
- **Found that urine uranium continues to be elevated in this cohort 12 years after first exposure**
- **Paper concludes that "no clinically significant uranium-related health effects were observed in blood count, blood chemistries, neuropsychological measures, semen quality, or genotoxicity measures."**

Epidemiologic Studies
Gulf War Veterans

McDiarmid et al, *Int Arch Occup Environ Health Aug 2005 [Epub]*

- **13 veterans with "high level" urine uranium (>0.10 ug/g creatine) and 19 with lower levels of urinary uranium (<0.10 ug/g creatine)**
- **Significant differences reported include:**
  - Serum phosphate levels (high)
  - Uranium levels sign assoc with neurocogn accuracy index (intellectual level)
- **Differences approaching significance include:**
  - Urine retinol binding protein (high)
  - Neurocognitive accuracy measure (more impairment)
  - Mutation frequencies
- **Low and high U groups had elevated serum prolactin levels**

Epidemiologic Studies
Gulf War Veterans

McDiarmid et al, *Int Arch Occup Environ Health Aug 2005 [Epub]*

- **Concerns:**
  - **Comparisons between "low urine uranium" and "high urine uranium" groups, not between those with/without uranium, or exposed/not exposed**
  - **Small sample limits ability to detect significant differences**
  - **Differences that are identified are minimized**
  - **No information on chronic symptoms, symptom complexes**
  - **No information on tumors**

Depleted Uranium: Information Considered by RAC in 2004-2005

- DU exposure levels/modeled health risks
- Animal studies
- Epidemiologic studies

DU: Summary of Information Considered

DU exposure levels/modeled health risks

- Experimental and modeled DU exposure levels generally indicate no/minimal expected increases in known health risks
- Models focused on expected risks associated with renal effects, common cancers

DU: Summary of Information Considered

Animal Studies

- All exposure routes produce renal toxicity at higher doses
- DU from embedded pellets, injected U accumulate in the brain differentially by region; long-term effects on synaptic potential/ excitability in hippocampus
- Embedded DU pellets associated with chromosomal and mutagenic changes associated with tumor development; immunological changes
- Ingested, injected uranium associated with short-term changes in dopamine levels, longer-term changes in behavioral measures
- Inhaled DU can produce systemic effects, neuroinflammation ; direct brain penetration enhanced by nasal inflammation

DU: Summary of Information Considered

Epidemiologic Studies

- Little information from the large epidemiologic studies
- Baltimore VA cohort study suggests veterans carrying DU shrapnel continue to excrete DU over time, possible alterations in cognitive function, kidney function, hormonal levels (prolactin, thyroxin)
- Baltimore study does not provide information on tumors, symptom rates, Gulf War multisymptom illness

Unanswered Questions
DU and the Health of Gulf War Veterans

- Reports and epi studies have not specifically addressed questions re: possible links between DU and multisymptom illnesses in Gulf War veterans
- Little epidemiologic information concerning possible association of DU exposure with cancer
- No research comparing health outcomes in DU-exposed to DU-not exposed populations

Recommendations?

Animal/Toxicological Research:

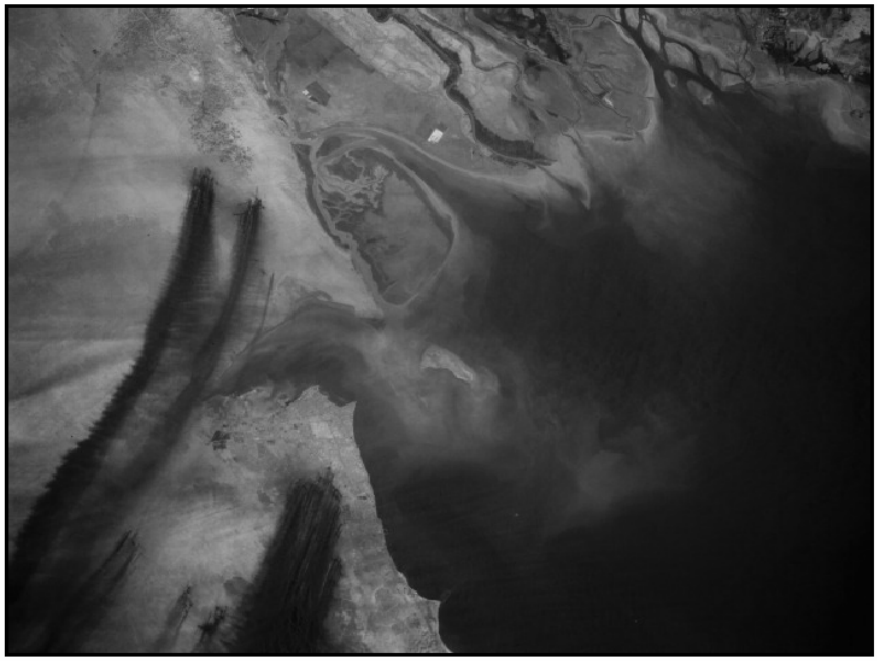
- **Carcinogenic effects, including brain tumors**
- **Neurotoxic effects: neurochemistry and behavioral studies**
- **Penetration and effects of inhaled exposures**

Epidemiologic Studies:

- **Expand epidemiologic research/surveillance of DU-exposed veterans**
  - e.g., 900 veterans with Level 1 and Level 2 exposures vs. nonexposed
  - e.g., existing data: map health outcomes with DU locations
- **Evaluate/report all health outcomes in expanded cohort:**
  - GWI symptom complex
  - Tumors, cancers
  - Lab measures

Presentation 3 – Lea Steele

Oil Well Fires, Petroleum Combustion



Hydrocarbon Fuel Combustion Products

Primary Sources of Exposure:

- Oil well fires (partially combusted crude oil)
- Tent heaters, cooking stoves (combusted gasoline, kerosene, diesel, jet fuel)
- Open burning of trash, wastes

Toxicants Associated with Petroleum Combustion

- Ozone (O_3)
- Nitrogen Dioxide (NO_2)
- Sulfur Dioxide (SO_2)
- Carbon Monoxide (CO)
- Hydrogen Sulfide (H_2S)
- VOCs: Volatile organic compounds *(benzene, toluene, etc)*
- PAHs: Polycyclic aromatic hydrocarbons *(anthracene, pyrene,etc)*
- Metals *(cadmium, chromium, lead, nickel, mercury, vanadium)*
- Acidic gases/aerosols *(hydrochloric acid, nitric acid, sulfuric acid)*
- Particulate matter *(PM_{10}, $PM_{2.5}$, ultrafine particles)*

IOM Report on Fuel, Combustion Products, and Propellants (2005)

Sufficient evidence to conclude that there is an association between combustion products and lung cancer

Limited/suggestive evidence of an association between combustion products and cancers of nasal and oral cavities, bladder cancer, and low birthweight/pre-term births

Oil Well Fires, Combustion Products: Information Considered by RAC in 2004-2005

- Projects to estimate levels of exposure to contaminants from oil well fires and tent heaters, expected health risks
- Epidemiologic/human studies to evaluate associations between exposures and health outcomes

Estimates of Exposure/ Modeled Health Risks

Oil Well Fires

Petroleum Combustion Exposures in the Gulf War: How Many Were Exposed?

Study	Population	Findings
Kang, 2000	11,441 US Gulf veterans	65% reported exposure to smoke from oil well fires 80% reported exposure to diesel, kerosene, petro fumes 30% consumed food contaminated w/ oil, smoke
Unwin, 1999	3,284 UK Gulf veterans	72% reported oil well fire smoke exposure 78% reported exposure to exhaust from heaters 84% reported exposure to diesel/petrochem fumes
Cherry, 2001	7,971 UK Gulf veterans	61% reported oil well fire exposure

Emissions from unvented tent heaters

- 2 studies from Lovelace Respiratory Research Institute
  - Zhou Y, Cheng YS. Aerosol Science and Technology 33:510-524 (2000)
  - Cheng YS, Zhou Y, et al. Aerosol Science and Technology 35: 949-957 (2001)
- Experiments simulated and characterized emissions from heaters used inside of Army tent
- Tested 3 types of heaters, 3 types of fuels (kerosene, JA-1, JP-8)

Emissions from unvented tent heaters

- **Results:**
  - **Emissions varied with type of fuel, type of heater, and temperature**
  - **Convection heaters emitted more NO and SO_2 then radiant heaters, less CO and particulates**
  - **NO_x, CO, and SO_2 exceeded air quality standards when tent doors were closed; but did not exceed 24-hour exposure standards**
  - **Most particulates were in the fine range (peak ~0.2 - 0.3 microns), with some in the ~10 micron range. Levels exceeded 24-hour standards when door closed, close to standards when door open**

Zhou Y, Cheng YS. Aerosol Science and Technology 33:510-524 (2000)

USACHPPM

Exposure to Smoke from the Kuwait Oil Well Fires

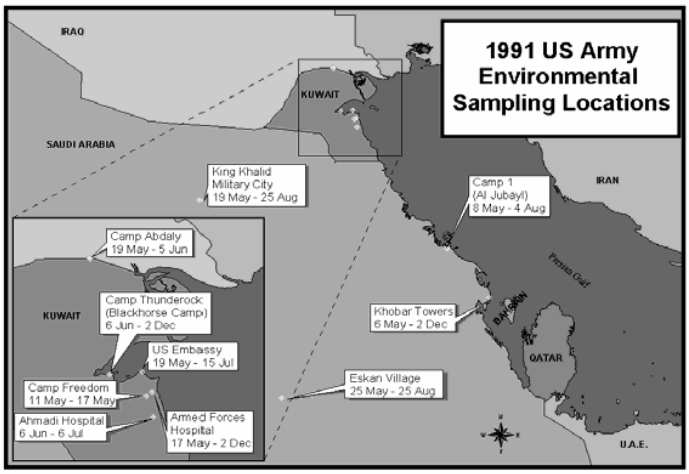
Presentation to

Research Advisory Committee on Gulf War Veterans' Illnesses

Mr. Jeffrey Kirkpatrick
Acting Program Manager
Global Threat Assessment
25 October 2004

Slide adapted from: Kirkpatrick J. Exposure to Smoke from the Kuwait Oil Well Fires. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Oct 25, 2004; Washington, DC.

1991 Oil Fires Sampling Locations



Slide adapted from: Kirkpatrick J. Exposure to Smoke from the Kuwait Oil Well Fires. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Oct 25, 2004; Washington, DC.

Slide adapted from: Heller JM. Overview of the Assessment of U.S. Forces Exposure to Oil Well Fire Emissions in the Persian Gulf in 1991. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Oct 25, 2004; Washington, DC.

Modeled Exposure Data

- Expands Oil Fires Assessment of:
  - **Time** (from May-Dec '91 to Feb-Nov '91)
  - **Location** (from 10 Specific Sites to Entire KTO)
  - **Population** (from Subset of Exposed Population to Entire Oil Fires Exposed Population)
  - **Sources** (Separates oil fire sources from industrial, vehicular and natural sources)

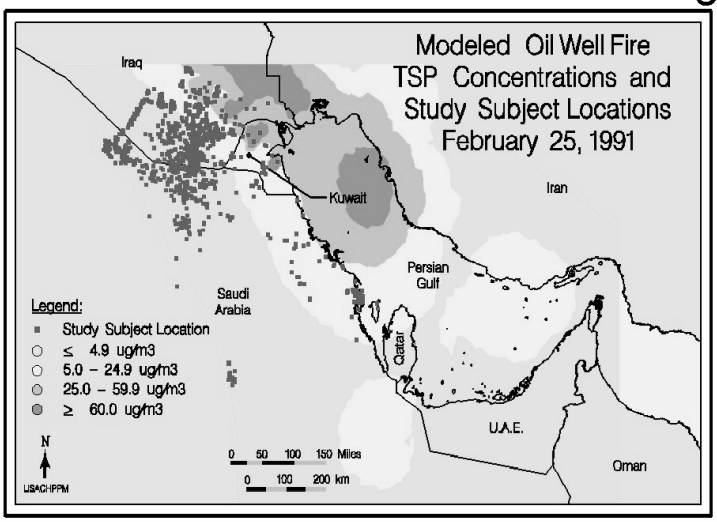
Slide adapted from: Kirkpatrick J. Exposure to Smoke from the Kuwait Oil Well Fires. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Oct 25, 2004; Washington, DC.

Modeled Pollutants of Concern

Volatile Organic Compounds		
Benzene	Toluene	m-Xylene
o-Xylene	p-Xylene	Propylbenzene
Ethylbenzene		
Polycyclic Aromatic Hydrocarbons		
Naphthalene		
Particulates, Metals, Inorganics		
Total Suspended Particulate	Iron	Nickel
Vanadium		

Slide adapted from: Kirkpatrick J. Exposure to Smoke from the Kuwait Oil Well Fires. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Oct 25, 2004; Washington, DC.

Oil Fires Particulate Matter Modeling



Slide adapted from: Kirkpatrick J. Exposure to Smoke from the Kuwait Oil Well Fires. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Oct 25, 2004; Washington, DC.

Oil Well Fires Emissions Modeling

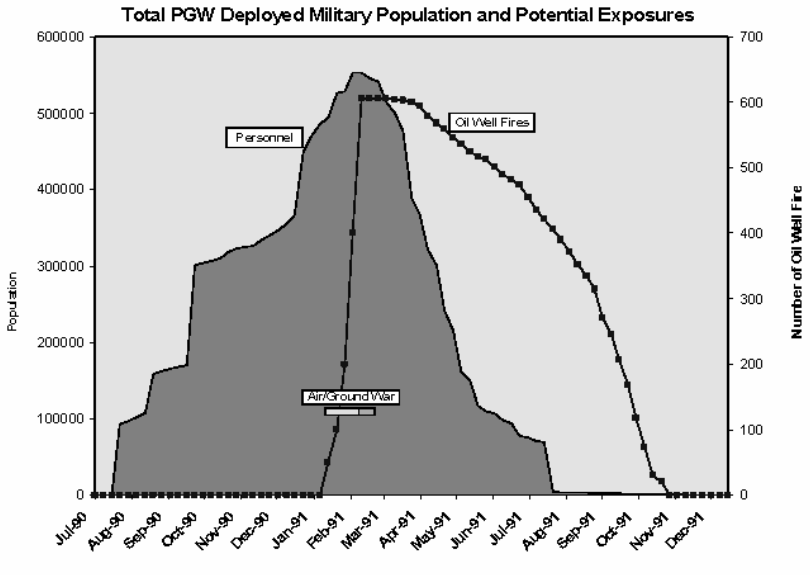
- Dispersion Modeling: NOAA ARL
  - HYSPLIT (Hybrid Single Particle Lagrangian Integrated Trajectory) Model
- Source Term Refinements
  - 24 Hour Unit Emission Concentration – Breathing Zone
  - Extinguishment Chronology
  - Smoke Lofting Feedback
- 15 Km Grid Spacing for Gulf War Theater (over 40,000 points)
- Meteorological Data:
  - National Weather Service; Medium Range Forecast Model
  - European Center for Medium Range Weather Forecasting (ECMWF)
- Air Concentrations Validated – Ground and Aircraft Measurements of SO_2 and Soot

Slide adapted from: Kirkpatrick J. Exposure to Smoke from the Kuwait Oil Well Fires. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Oct 25, 2004; Washington, DC.

Troop Location Information and Database

Unit Movement Data
Persian Gulf War Registry
Oil Well Fires Web Page

Slide adapted from: Wortman W. Troop Location Information and Database. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Oct 25, 2004; Washington, DC.



Slide adapted from: Wortman W. Troop Location Information and Database. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Oct 25, 2004; Washington, DC.

General Health Risk


DEPLOYMENT ENVIRONMENTAL SURVEILLANCE PROGRAM

Gulf War Fires

USACHPPM

Individual Oil Well Fire Smoke Exposure Risk

The U.S. Army Center for Health Promotion and Preventive Medicine located in Aberdeen Proving Ground, Maryland is responsible for assessing the environmental health risk of our deployed forces. We determined your exposure to Oil Well Fire Smoke based on data showing that you were in theater from 1/1/1991 to 4/30/1991 with the 0475 MEDICAL HOSPITAL MASH.
The table below shows your oil fire smoke exposure.

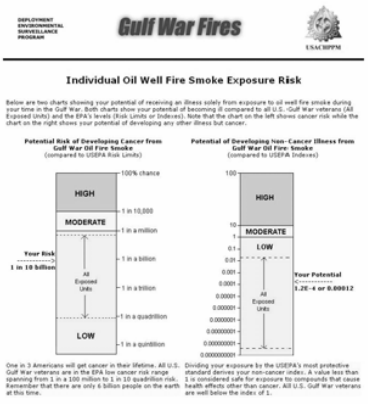
9/13/2004
900-00-0024

Factor	Potential Illness
Extra chance of getting cancer.	Low
Extra chance of getting an illness other than cancer.	Low

Potential Illness Charts

Slide adapted from: Wortman W. Troop Location Information and Database. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Oct 25, 2004; Washington, DC.

Cancer/Non-Cancer Risk


DEPLOYMENT ENVIRONMENTAL SURVEILLANCE PROGRAM

Gulf War Fires

USACHPPM

Individual Oil Well Fire Smoke Exposure Risk

Below are two charts showing your potential of receiving an illness solely from exposure to oil well fire smoke during your time in the Gulf War. Both charts show your potential of becoming ill compared to all U.S.-Gulf War veterans (All Exposed Units) and the EPA's levels (Risk Limits or Indexes). Note that the chart on the left shows cancer risk while the chart on the right shows your potential of developing any other illness but cancer.

Potential Risk of Developing Cancer from Gulf War Oil Fire Smoke
(compared to USEPA Risk Limits)

100% chance
HIGH
1 in 10,000
MODERATE
1 in a million
Your Risk
1 in 10 billion
All Exposed Units
1 in a billion
1 in a trillion
1 in a quadrillion
LOW
1 in a quintillion

One in 3 Americans will get cancer in their lifetime. All U.S. Gulf War veterans are in the EPA low cancer risk range spanning from 1 in a 100 million to 1 in 10 quadrillion risk. Remember that there are only 6 billion people on the earth at this time.

Potential of Developing Non-Cancer Illness from Gulf War Oil Fire Smoke
(compared to USEPA Indexes)

100
HIGH
10
MODERATE
1
LOW
0.1
0.01
0.001
0.0001
0.00001
0.000001
0.0000001
0.00000001
0.000000001
All Exposed Units
Your Potential
1.2E-4 or 0.00012

Dividing your exposure by the USEPA's most protective standard derives your non-cancer index. A value less than 1 is considered safe for exposure to compounds that cause health effects other than cancer. All U.S. Gulf War veterans are well below the index of 1.

Slide adapted from: Wortman W. Troop Location Information and Database. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Oct 25, 2004; Washington, DC.

Overview of the Assessment of U.S. Forces Exposure to Oil Well Fire Emissions in the Persian Gulf in 1991

25 October 2004

Jack M. Heller, Ph.D.
Director Health Risk Management

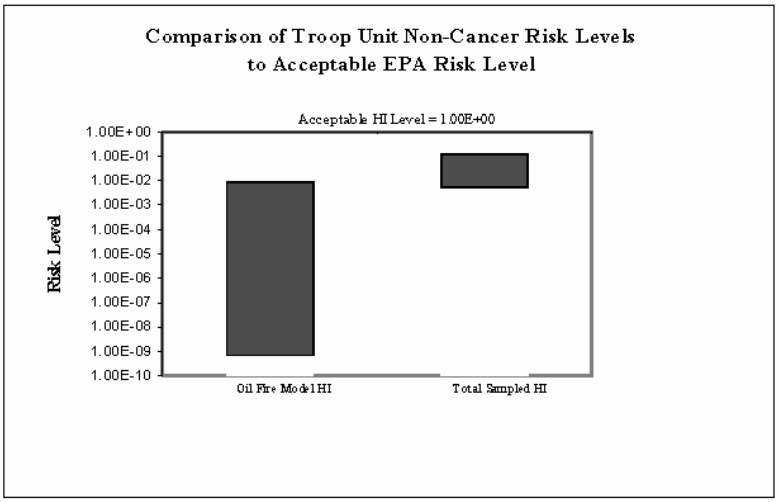
Slide adapted from: Heller JM. Overview of the Assessment of U.S. Forces Exposure to Oil Well Fire Emissions in the Persian Gulf in 1991. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Oct 25, 2004; Washington, DC.

Risk Characterization

- Carcinogenic Risk = Intake X Slope Factor
  - USEPA Acceptable Range (1E-04 to 1E-06)
- Non-Carcinogenic Risk = Intake / Reference Dose (Hazard Quotient)
  - USEPA Acceptable Level (1)
  - Segregate Chemicals by Mechanism of Action / Target Organ
- Total Risk
  - Additive for Chemicals and Pathways

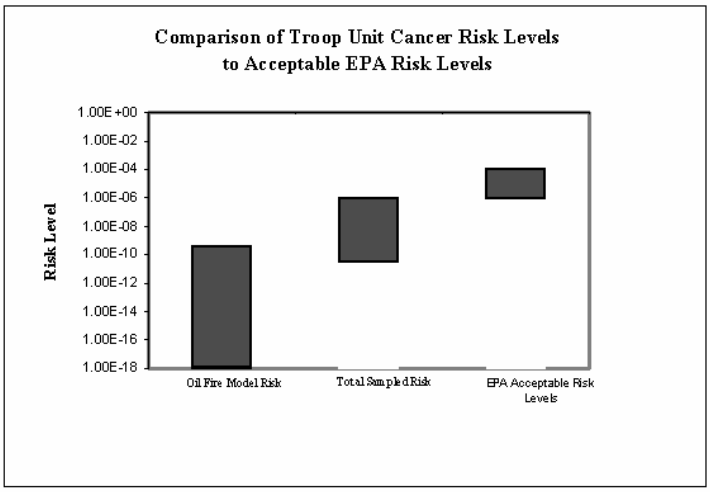
Slide adapted from: Heller JM. Overview of the Assessment of U.S. Forces Exposure to Oil Well Fire Emissions in the Persian Gulf in 1991. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Oct 25, 2004; Washington, DC.

Non-Cancer Comparison



Slide adapted from: Heller JM. Overview of the Assessment of U.S. Forces Exposure to Oil Well Fire Emissions in the Persian Gulf in 1991. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Oct 25, 2004; Washington, DC.

Excess Cancer Comparison



Slide adapted from: Heller JM. Overview of the Assessment of U.S. Forces Exposure to Oil Well Fire Emissions in the Persian Gulf in 1991. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Oct 25, 2004; Washington, DC.

Human Studies: Associations between Petroleum Combustion Products and Health Outcomes

Oil Well Fires, Petroleum Combustion

Emissions from Tent Heaters: Health Outcomes

Study	Outcome	Exposure	Findings
Proctor, 1998 (220 Army vets)	symptoms (groups)	smoke from tent heaters	Sign. correlated with cardiac, neurological, and pulmonary symptoms ($p<0.001$)
Unwin, 1999 (3,284 UK vets)	CMI	exhaust from heaters	OR = 1.9 (1.6-2.2)
Spencer, 2001 (1,119 OR/WA vets)	CMI	diesel heater kerosene heater potbelly heater cleaned heaters	OR = 1.78 (0.93-3.42) OR = 1.92 (0.93-4.00) OR = 2.31 (1.14-4.66) OR = 2.41 (1.29-4.52)
Gray, 2002 (11,868 Seabees)	GWI	jet fuel burned in tent heaters	OR = 2.12 (1.81-2.49) (unadj) OR = 1.11 (0.88-1.39) (saturated)
Wolfe, 2002 (945 Army vets)	CMI	heater in tent	OR = 1.6 (1.0-2.5)

Exposure to Oil Well Fire Smoke: Symptom Complexes

Study	Exposure	Outcome	Findings
Iowa Study, 1997 (1,886 Iowa vets)	s/r smoke, combustion products	cogn dysf symps FMS symps depression symps	sign prev diff (p<0.001) sign prev diff (p<0.001) sign prev diff (p<0.001)
Haley, 1997 (249 Navy vets)	s/r oil smoke	any of 3 syndromes	ns
	scaled smoke exposure	Syndrome 2	p = 0.02
Nisenbaum, 2000 (1,163 Air Guard vets)	s/r	mild-mod CMI severe CMI	OR = 1.29 (0.92-1.81) OR = 1.62 (0.79-3.35)
Spencer, 2001 (1,119 OR, WA vets)	eye irritation from burning oil wells	CMI	1-5 days: OR = 2.64 (1.34-5.20) 6 + days: OR = 4.47 (2.07-9.63)

Exposure to Oil Well Fire Smoke: Symptom Complexes

Study	Exposure	Outcome	Findings
Unwin, 1999 (3,284 UK vets)	s/r	CMI	OR = 1.8 (1.5-2.1)
Wolfe, 2002 (945 Army vets)	s/r oil fire smoke odor	CMI	OR = 2.1 (1.4-3.2)
Gray, 2002 (11,868 Seabees)	modeled	GWI	bivariate: OR = 1.54 (1.31-1.80) multivar: OR = 0.44 (0.26-0.73)
	self-report		bivariate: OR = 2.22 (1.85-2.66) (s/r) multivar: OR = 1.23 (0.91-1.65) (s/r)
Kang, 2002	consumed food contaminated with oil, smoke	Neuro symp factor	73% cases vs. 21% controls

Did Exposure to Oil Well Fire Smoke During the Gulf War Increase the Risk of Asthma among Veterans? A Review of Three Studies

David N. Cowan, PhD, MPH

Division of Preventive Medicine
Walter Reed Army Institute of Research
Silver Spring, MD

EPICON Associates, LLC
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Formerly with
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Walter Reed Army Medical Center
Washington, DC

Slide adapted from: Cowan DN. Did Exposure to Oil Well Fire Smoke During the Gulf War Increase the Risk of Asthma among Veterans? A Review of Three Studies. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Oct 25, 2004; Washington, DC.

A case control study of asthma among U.S. Army Gulf War veterans and modeled exposure to oil well fire smoke

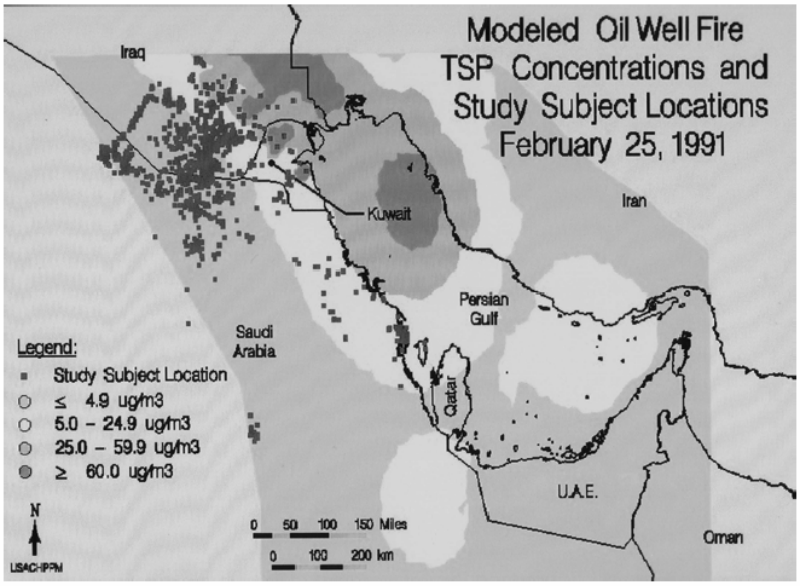
David N. Cowan, Jeffrey L. Lange, Jack Heller,
Jeff Kirkpatrick, Samar DeBakey
Mil Med 2002 Sep;167(9):777-82

Slide adapted from: Cowan DN. Did Exposure to Oil Well Fire Smoke During the Gulf War Increase the Risk of Asthma among Veterans? A Review of Three Studies. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Oct 25, 2004; Washington, DC.

Two 2002 Studies of Asthma and Exposure to Oil Well Fire Smoke

- **Smith TC, Heller JM, Hooper TI, Gackstetter GD, Gray GC. Are Gulf War veterans experiencing illness due to exposure to smoke from Kuwait oil well fires? Examination of Department of Defense hospitalization data. Am J Epidemiol 2002 May 15;155(10):908-17**
- **Lange JL, Schwartz DA, Doebbeling BN, Heller JM, Thorne PS. Exposures to the Kuwait oil fires and their association with asthma and bronchitis among gulf war veterans. Environ Health Perspect 2002 Nov;110(11):1141-6**

Slide adapted from: Cowan DN. Did Exposure to Oil Well Fire Smoke During the Gulf War Increase the Risk of Asthma among Veterans? A Review of Three Studies. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Oct 25, 2004; Washington, DC.



Slide adapted from: Cowan DN. Did Exposure to Oil Well Fire Smoke During the Gulf War Increase the Risk of Asthma among Veterans? A Review of Three Studies. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Oct 25, 2004; Washington, DC.

Comparison of exposures

- **Poor agreement between self-reported and modeled exposures (kappas of 0.13 and 0.12)**
- **High correlation between modeled cumulative exposure and days exposed to high (r_s=0.84)**

Slide adapted from: Cowan DN. Did Exposure to Oil Well Fire Smoke During the Gulf War Increase the Risk of Asthma among Veterans? A Review of Three Studies. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Oct 25, 2004; Washington, DC.

Table 4. Adjusted* Odds Ratios for Associations with Measures of Smoke Exposure

Cumulative exposure mg/m^3-days	
Categories	Adjusted Odds Ratio (95% CI)
< 0.1	1.00 (referent)
>= 0.1 – < 1.0	1.24 (1.00 – 1.55)
>= 1.0	1.40 (1.11 – 1.75)
Continuous	1.08 (1.01 – 1.15)

**Adjusted for sex, age, race/ethnicity, rank, smoking history, and self-reported exposure.*

Slide adapted from: Cowan DN. Did Exposure to Oil Well Fire Smoke During the Gulf War Increase the Risk of Asthma among Veterans? A Review of Three Studies. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Oct 25, 2004; Washington, DC.

Table 4. (Cont) Adjusted* Odds Ratios for Associations with Measures of Smoke Exposure

Days with Exposure >= 65 ug/m^3	
Categories	**Adjusted Odds Ratio (95% CI)**
0	1.00 (referent)
1-5	1.22 (0.99 – 1.51)
6-30	1.41 (1.12 – 1.77)
Continuous	1.03 (1.01 – 1.05)
**Adjusted for sex, age, race/ethnicity, rank, smoking history, and self-reported exposure.*	

Slide adapted from: Cowan DN. Did Exposure to Oil Well Fire Smoke During the Gulf War Increase the Risk of Asthma among Veterans? A Review of Three Studies. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Oct 25, 2004; Washington, DC.

Discussion

- We found significant associations between modeled smoke exposure and physician-diagnosed asthma for both cumulative exposure measures defined *a priori*
- We found dose-responses for both when considered as categorical measures and as continuous measures

Slide adapted from: Cowan DN. Did Exposure to Oil Well Fire Smoke During the Gulf War Increase the Risk of Asthma among Veterans? A Review of Three Studies. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Oct 25, 2004; Washington, DC.

What did they find?

- Smith, et al. No association between modeled smoke exposure (MSE) and hospitalization for asthma (and other diseases)
- Lange, et al. No association between MSE and self-reported asthma symptoms

Slide adapted from: Cowan DN. Did Exposure to Oil Well Fire Smoke During the Gulf War Increase the Risk of Asthma among Veterans? A Review of Three Studies. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Oct 25, 2004; Washington, DC.

Diagnostic specificity and sensitivity

- Smith, et al., used only hospitalized cases, likely missed 90% of all cases (high PPV, not sensitive)
- Lange, et al., used self-report, likely included many non-cases (low PPV, not specific)
- Classification error for both
- Cowan, et al., used physician dx, sensitivity and specificity unknown.

Slide adapted from: Cowan DN. Did Exposure to Oil Well Fire Smoke During the Gulf War Increase the Risk of Asthma among Veterans? A Review of Three Studies. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Oct 25, 2004; Washington, DC.

More comments on non-differential misclassification

- "...the attenuation (of the odds ratio) can be appreciable even with a high sensitivity and specificity." Armstrong, et al. *Principles of Exposure Measurement in Epidemiology*
- "Random misclassification always results in an underestimation of the true relative risk..." Hennekins and Buring, *Epidemiology in Medicine*

Slide adapted from: Cowan DN. Did Exposure to Oil Well Fire Smoke During the Gulf War Increase the Risk of Asthma among Veterans? A Review of Three Studies. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Oct 25, 2004; Washington, DC.

Conclusions

- When the observed odds ratios from the Cowan, et al., study are considered in the light of the substantial opportunity for misclassification, the findings are suggestive of an association between objective estimates of exposure to oil well fire smoke and risk of asthma diagnosis among CCEP participants
- Smith, et al., and Lange, et al., are likely to have even higher levels of misclassification, and that may account for the findings of no association
- More studies needed...

Slide adapted from: Cowan DN. Did Exposure to Oil Well Fire Smoke During the Gulf War Increase the Risk of Asthma among Veterans? A Review of Three Studies. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Oct 25, 2004; Washington, DC.

Exposure to Oil Well Fire Smoke: Diagnosed Conditions

Study	Exposure	Outcome	Findings
Gray, 2002 (11,868 Seabees)	CHPPM models	self-reported medical diagnoses	Asthma OR = 1.82 (1.23-2.69) Bronchitis OR = 1.49 (1.18-1.87)
Cowan, 2002 (873 cases, 2464 controls from CCEP)	s/r and CHPPM models	clinically diagnosed	Asthma OR = 1.4 (1.1 – 1.8)
Lange, 2002 (1,560 Iowa veterans)	s/r CHPPM models	symptoms of asthma, bronchitis	Asthma ORs = 1.77-2.83 (s/r) Bronchitis ORs = 2.14-4.78 (s/r) Asthma, Bronchitis: ORs= 0.77-1.26
Kelsall, 2004 (1,456 Australian vets)	s/r exposure to "SMOIL"	self-reported medical diagnoses	Asthma OR = 1.82 (1.23-2.69) Bronchitis OR = 1.49 (1.18-1.87)

Gulf Veterans vs. Not Deployed: Diagnosed Conditions

Study	Exposure	Outcome	Findings
Unwin, 1999 (3,284 UK vets)	PGW vs. nondeployed	self-reported medical dx	Asthma OR = 1.8 (1.4-2.4) Bronchitis OR = 1.7 (1.2-2.3)
Iowa Study, 1997 (1,886 Iowa vets)	PGW vs. nondeployed	symptoms suggesting dx	Asthma sign. prev difference Bronchitis sign. prev difference
Steele, 2001 (2,031 Kansas vets)	PGW vs. nondeployed	self-reported medical dx	Asthma OR = 2.08 (1.02-4.26) Bronchitis OR = 2.61 (1.53-4.47)
Gray, 2002 (11,868 Seabees)	PGW vs. nondeployed	self-reported medical dx	Asthma OR = 1.82 (1.23-2.69)
Goss-Gilroy, 1997 (Canadian vets)	PGW vs. nondeployed	symptoms suggesting dx	Asthma OR = 2.64 (1.97-3.55) Bronchitis OR = 2.81 (2.22-3.55)
Kelsall, 2004 (1,456 Australian vets)	PGW vs. nondeployed	self-reported medical dx	Asthma OR = 1.2 (0.8-1.8) Bronchitis OR = 1.1 (0.9-1.5)

Summary of Epidemiologic Findings: Oil Well Fire Smoke

- Among veterans who served in the Gulf War, exposure to oil fire smoke associated with:
  - Diagnosed and self-reported asthma (ORs~1.4 - 2.8)
  - Chronic multisymptom conditions (ORs~1.5 - 4.5) (possible dose-response effect—proximity and duration)

Tours of Duty

- **Late February 1991 through 11-8-91**
- **Work day 10 – 12 hours**
- **Tour 28 – 40 days alternated with 28 day leave**

Slide adapted from: Friedman GK. Medical Outcomes of Oil Well Firefighters – Kuwait. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Sep 19, 2005; Washington, DC.

Tours of Duty

- Adair – 39 men - avg. 98 days
- Wild Well – 38 men avg. 98 days
- Boots and Coots – 30 men avg 112 days
- Average – 105 days

Slide adapted from: Friedman GK. Medical Outcomes of Oil Well Firefighters – Kuwait. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Sep 19, 2005; Washington, DC.

Texas Based Oil Well Fighters

- Extinguished the majority of the wells
- The largest oil fields
- High pressure wells with the largest flow of gas and oil and the largest plumes
- Longest exposure times

Slide adapted from: Friedman GK. Medical Outcomes of Oil Well Firefighters – Kuwait. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Sep 19, 2005; Washington, DC.

LIVING CONDITIONS

Lived within 2 miles of the burning fields in an abandoned complex between Burqan and Ahmadi Oil fields

Initially no running water (trucked in)

Smoke filled building

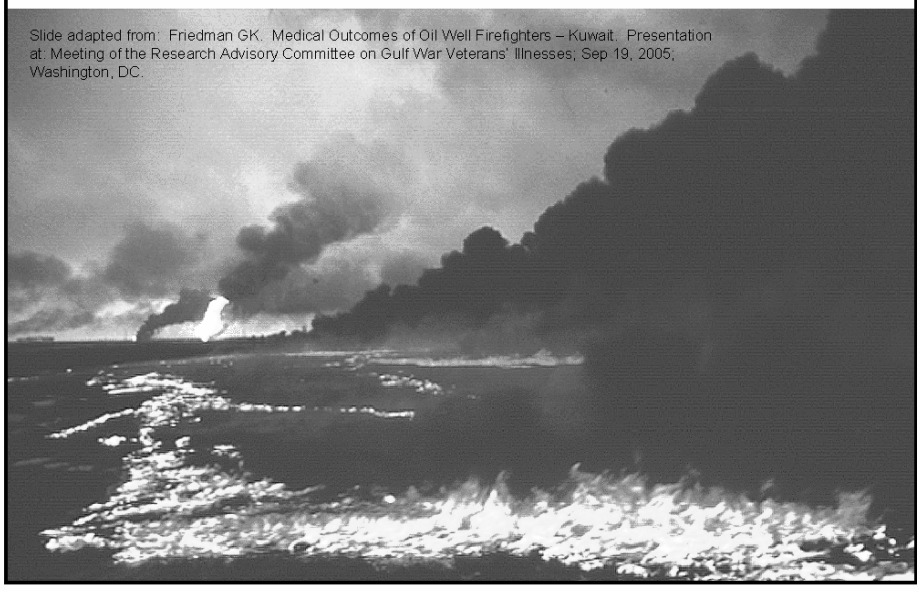
Slide adapted from: Friedman GK. Medical Outcomes of Oil Well Firefighters – Kuwait. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Sep 19, 2005; Washington, DC.

FIREFIGHTER PROTECTIVE GEAR

Nomex underwear
Gloves
Hard hat
Leather boots
Work coveralls
No respirators

Slide adapted from: Friedman GK. Medical Outcomes of Oil Well Firefighters – Kuwait. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Sep 19, 2005; Washington, DC.

Burning Oil Lake



MEDICAL SURVEILLANCE

- Complete history and physical – physician Board Certified in Occupational Medicine and Internal Medicine
- CBC
- SMA-20 (glucose, BUN, Creatinine, Liver enzymes, etc.)
- Urinalysis

Slide adapted from: Friedman GK. Medical Outcomes of Oil Well Firefighters – Kuwait. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Sep 19, 2005; Washington, DC.

MEDICAL SURVEILLANCE

- Pulmonary function testing (spirometry)
- Chest x-ray
- EKG
- Stool for O&P (as available or indicated)

Slide adapted from: Friedman GK. Medical Outcomes of Oil Well Firefighters – Kuwait. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Sep 19, 2005; Washington, DC.

MEDICAL SURVEILLANCE

- Firefighters were re-evaluated during leaves between their tours of duty
- A follow up in 1994 with each of the 3 Houston based companies revealed no claims for medical problems arising from service in Kuwait.

Slide adapted from: Friedman GK. Medical Outcomes of Oil Well Firefighters – Kuwait. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Sep 19, 2005; Washington, DC.

SUMMARY

No significant illnesses have been reported from this cohort. Specifically no complaints resembling "Gulf War Syndrome"

Slide adapted from: Friedman GK. Medical Outcomes of Oil Well Firefighters – Kuwait. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Sep 19, 2005; Washington, DC.

Current Status 9-14-05

Telephone conference with both Boots and Coots and Wild Well Control reveals no reports of Gulf War Syndrome-type illness or other chronic illness or injury arising from the Kuwait experience. Firefighters have been sent to Iraq during the current conflict without incidence.

Slide adapted from: Friedman GK. Medical Outcomes of Oil Well Firefighters – Kuwait. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Sep 19, 2005; Washington, DC.

Refinery Fire

Slide adapted from: Friedman GK. Medical Outcomes of Oil Well Firefighters – Kuwait. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Sep 19, 2005; Washington, DC.

During the past 25 years evaluation of thousands of Texas refinery and chemical plant workers exposed to crude oil, and its products of combustion have failed to reveal a pattern similar to "Gulf War Syndrome" in a civilian population.

Slide adapted from: Friedman GK. Medical Outcomes of Oil Well Firefighters – Kuwait. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Sep 19, 2005; Washington, DC.

Raw or burning crude oil should be dismissed as a cause for Gulf War Syndrome

Slide adapted from: Friedman GK. Medical Outcomes of Oil Well Firefighters – Kuwait. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Sep 19, 2005; Washington, DC.

Petroleum Combustion Products: Information Considered by RAC in 2004-2005

- Oil fire, petroleum combustion exposures, modeled health risks
- Human studies

Oil Well Fires, Combustion Products

Measured/Modeled Exposures

- Modeled exposure assessments consistently suggest no oil fire-related exposures that exceed air quality standards except particulates; no expected increases in cancer, other health problems
- Measured exposures did not provide information on oil fire emissions close to the burning well, or in the weeks and months when exposures were highest
- Modeled tent heater emissions exceed standards for particulates, also high for NO_x, CO_x, SO_2

Oil Well Fires, Combustion Products

Human Studies

- Clinical study indicates modeled oil well fire smoke exposure associated with sign. increased rate of physician-dx asthma
- Epidemiologic studies suggest self-reported oil fire exposure associated with:
  - dx and self-reported asthma (ORs~1.4 - 2.8)
  - Chronic multisymptom illness (ORs~1.5 - 4.5)
    (possible dose-response effect—proximity and duration)
- Epidemiologic studies suggest self-reported tent heater exposure associated with:
  - Chronic multisymptom illness (ORs~2.0), other symptom groups

Oil Well Fires, Combustion Products and the Health of Gulf War Veterans: Remaining Questions

- Is Gulf War-related multisymptom illness linked to exposure to smoke from oil well fires?
  - *As a cofactor with other exposures? (no animal studies or epidemiologic analyses have evaluated oil fires in combination with other exposures)*
  - *Identified associations between oil fires and GWI accurate or due to effects of confounding? bias?*
- Are increased rates of asthma or other diagnosed conditions associated with exposure to oil well fire smoke?
- Associations between tent heater emissions and GWI?

Oil Well Fires, Combustion Products and the Health of Gulf War Veterans: Remaining Questions

- Additional health concerns for military personnel located very close to burning wells for an extended period?
  - This concern s/w diminished by reports on civilian firefighters
- Additional health concerns for veterans who may have been more vulnerable to effects of combustion emissions, particulates?

Discussion of Recommendations

Animal/Toxicological Research:

Epidemiologic Studies:

- Determine whether asthma, chronic respiratory dx associated with Gulf War service generally, and with oil fire exposure
- Clarify possible association of GWI with oil well fire smoke and tent heaters in existing epi studies
  - Increased GWI risk in combination with other exposures?
  - Does association diminish when controlling for other exposures?
- ? Epi study to evaluate health effects on subgroup of Gulf veterans with most intense exposure to oil well fires?

Presentation 4 – Lea Steele

Vaccines

★☆★ RAC-GWVI

IOM Conclusions

- IOM report 2002: AVA effective & acceptably safe
- Cochrane Collaboration: Safe & Effective; No need for additional study unless new vaccine

Vaccines: Information Considered by RAC

- Exposures: information on vaccines received
  - Studies, reports of vaccine safety/efficacy
  - Information on vaccine components
- Animal Studies
- Epidemiologic studies evaluating associations between vaccines and health outcomes in Gulf War veterans

★☆★ RAC-GWVI

Information Considered by the Committee Prior to 2004 RAC Report

- Overview of epidemiologic findings re: vaccines
- Overview of components of anthrax vaccines
- U.K. and U.S. AVA contain different "ingredients", were administered differently; primary similarity is the active antigen
- Clinical studies of "next generation" anthrax vaccines include arms in which AVA is administered to study subjects
- RAC 2004 Recs:
  - *Include evaluation of chronic symptoms similar to GWI in AVA trials*
  - *Conduct retrospective studies of long-term effects of AVA related to military's mandatory AVIP*

★☆★ RAC-GWVI

Types of Vaccines Received, Information on Safety/Efficacy

Vaccines

★☆★ RAC-GWVI
Research Advisory Committee On Gulf War Veterans' Illnesses

Vaccines Administered to U.S. Military Personnel 1990-1991

IMMUNIZING AGENT	ARMY	NAVY	AIR FORCE	MARINE CORPS	COAST GUARD
Adenovirus (types 4 and 7)	B	B	B	B	H
Cholera	F	F	F	F	F
Hepatitis B	B,G,H	B,G,H	B,G,H	B,G,H	G,H
Influenza	A,B,R	A,B,R	A,B,R	A,B,R	B,G,H
Measles	B,G	B,G	B,G	B,G	B,G
Meningococcal (A,C,Y,W-135)	B,H	B,H	B,H	B,H	B,H
Mumps	G,H	G,H	G,H	G,H	G
Plague	C,D,E,G	D,G	E	A,G	E
Polio	A,R	A,R	A,R	A,R	A
Rabies	D,G,H	D,G,H	D,G,H	D,G,H	H
Rubella	B,G	B,G	B,G	B,G	B
Smallpox	B,H	B,H	B,H	B,H	B,H
Tetanus-diphtheria	A,B,R	A,B,R	A,B,R	A,B,R	A,B
Typhoid	C,E,H	H	C,E,H	H	E
Yellow fever	C,D,E	A,R	C,E	A,R	B,E

F: All active duty personnel

B: Recruits

C: Navy divers

D: Special Operating Forces components

E: When deploying or travelling to high risk areas

F: Only when routine by host country directive

G: High risk occupational groups

H: As directed by applicable Surgeon General

R: Reserve components

X: Reserve personnel active 30 days during the season

Vaccines received in association with Gulf War Service

- Most personnel received multiple vaccines prior to deployment
  - Number varied
  - Specific types varied by branch, prior vaccine history
- Some shots given in theater
  - Most prominently gamma globulin, anthrax, botulinum toxoid vaccines
- Greatest attention/concern raised re: possible adverse effects of anthrax vaccine, multiple vaccinations

★☆★ RAC-GWVI

20 Studies to Evaluate Adverse Events After Anthrax Immunization

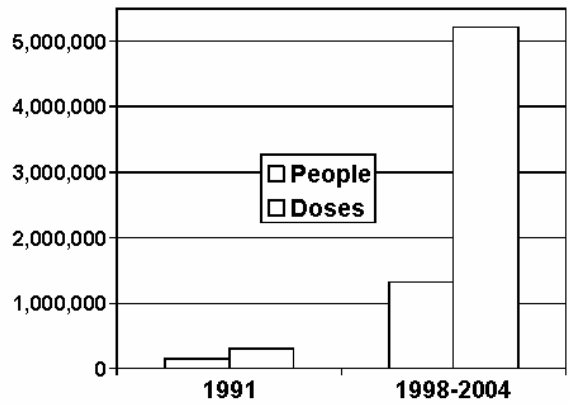
7 Apr 05

COL John D. Grabenstein, RPh, PhD, U.S. Army

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

Slide adapted from: Grabenstein JD. 20 Studies to Evaluate Adverse Events After Anthrax Immunization. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Apr 7, 2005; Washington, DC.

Anthrax Vaccinees and Vaccinations



Slide adapted from: Grabenstein JD. 20 Studies to Evaluate Adverse Events After Anthrax Immunization. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Apr 7, 2005; Washington, DC.

Anthrax Vaccine Safety Surveillance

- Mar 98 to Oct 04, > 5.2 million doses of anthrax vaccine to > 1.3 million people.
- Soreness, redness, itching, swelling at injection site:
  - Less than 2.5 cm: 30% of men, 60% of women.
  - More than 12 cm: 1% to 2%, both genders
  - Inject over deltoid **(not triceps)**
- Lump at injection site common, lasts a few weeks, goes away.
- Systemic symptoms—muscle or joint aches, headaches, rashes, chills, low-grade fever, nausea.
  - 5% to 35%, like other vaccines

Slide adapted from: Grabenstein JD. 20 Studies to Evaluate Adverse Events After Anthrax Immunization. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Apr 7, 2005; Washington, DC.

Anthrax Vaccine Safety Litany

	Vaccinees
Brachman Study, *Am J Public Health* 1962	379
CDC Observational Study, *Fed Reg* 1985	6,986
Ft Detrick Multi-Vaccine Studies, *BJHH* '58, *Ann Intern Med* 1965, 1974	99
Ft Detrick Long-Term Health Study, Vaccine 2004	142
Fort Bragg Booster Study (after Persian Gulf War), *Vaccine* 2002	495
USAMRIID Reduced-Dose / Route-Change Study, *Vaccine* 2002	173
Fort Detrick Special Immunization Program, *Vaccine* 2001	1,583
Canadian Forces Safety Evaluation, *Military Medicine* 2004	403
TAMC-601 Survey, *MMWR* 2000; 49:341-5, *J Occup Environ Med* 2003	601
US Forces Korea Records, *MMWR* 2000; 49:341-5, *Vaccine* 2003	2,824
VAERS review by AVEC, *Pharmacoepidemiol & Drug Safety* 2002, 2004	1,623
ROTC Cadets, Ft Lewis, *Med Surveil Mon Rep* 2001	73
USAF Air Combat Command Study, *Military Medicine* 2002	4,045
Fort Stewart Pregnancy Study, *JAMA* 2002	4,092
Army Disability Discharge Claims Database, *J Occup Envir Med* 2004	154,456
USAF Visual Acuity Study	958
Aviator Flight Physical Examinations	3,356
DMSS Hospitalization Cohort Study, *Vaccine* 2002	757,540 py
NHRC Hospitalization Cohort Study, *Vaccine* 2002	120,870 py
Male Fertility Study (sperm parameters), Fertility & Sterility 2005	254
Mycoplasma Study, *Emerging Infectious Diseases* 2002	(laboratory)

Slide adapted from: Grabenstein JD. 20 Studies to Evaluate Adverse Events After Anthrax Immunization. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Apr 7, 2005; Washington, DC.

Disability Discharge Evaluations

- Sulsky SI, **et al. Disability among U.S. Army personnel vaccinated against anthrax. *Journal Occupational & Environmental Med* 2004;46:1065-1075.**
- Subjects: **U.S. Army personnel receiving ≥ 1 dose of anthrax vaccine adsorbed (AVA) between Mar 98 and Feb 02 vis-à-vis disability evaluation.**
- Methods: **29,332 disability evaluations among 716,833 active-duty Soldiers (154,456 vaccinated) over 4.25 years. Cox proportional-hazard models for risk of disability evaluation.**
- Results: **Adjusted hazard ratio (HR) 0.96 (95% CI: 0.92, 0.99). Unadjusted rates: 140 per 100,000 person-months if unvaccinated, 68 per 100,000 person-months if anthrax-vaccinated.**
- **Separate adjusted HRs for men, women, permanent and temporary disability, musculoskeletal and neurological conditions similar, 0.90 to 1.04. Latency assumptions did not affect results.**
- Conclusion: **Anthrax vaccination does not increase risk of disability evaluation, nor granting of disability finding.**

Slide adapted from: Grabenstein JD. 20 Studies to Evaluate Adverse Events After Anthrax Immunization. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Apr 7, 2005; Washington, DC.

Squalene as an Adjuvant

Squalene is an oil. Produced in human liver, required for life.

Squalene naturally present in blood at 250 parts per billion (ppb). Fingerprint oils. Food. Supplements (olive oil).

Squalene alone may induce antibodies, but it is not an adjuvant (help antigens) by itself.

Squalene needs to be in the form of an emulsion (like mayonnaise) to be an adjuvant.

To be an adjuvant, squalene needs to be present at 1% to 5% 10,000,000 parts per billion (1%) to 50,000,000 parts per billion (5%)

***FluAd* (Italian influenza vaccine), given to > 10 million people, contains MF59 adjuvant, which includes 1.95% squalene, 19,500,000 parts per billion**

Slide adapted from: Grabenstein JD. 20 Studies to Evaluate Adverse Events After Anthrax Immunization. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Apr 7, 2005; Washington, DC.

Squalene and Squalene Tests

A. SRI tests 17 lots of anthrax vaccine, all negative. Test capable of detecting as little as 140 ppb. Spanggord et al, 2002

B. FDA tests 3 vaccines: diphtheria, tetanus, anthrax. Finds squalene in each at 10 to 83 ppb. Tells Congress: "trace, naturally occurring, safe"

C. SRI improves test. Tests 33 lots: no squalene in 32 lots. Squalene in one lot at 1 to 9 parts per billion, or 1 to 9 parts per 1,000,000,000. Manuscript in progress.

Summary: Squalene not added as adjuvant to any US-licensed vaccine. Trace quantities may be present, concentration less than naturally present in human blood

Slide adapted from: Grabenstein JD. 20 Studies to Evaluate Adverse Events After Anthrax Immunization. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Apr 7, 2005; Washington, DC.

Slide adapted from: Grabenstein JD. 20 Studies to Evaluate Adverse Events After Anthrax Immunization. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Apr 7, 2005; Washington, DC.

USAMRIID

Studies on the Health Effects of Multiple Vaccines: Completed and Ongoing

Research Advisory Committee on Gulf War Illness Meeting
U.S. Department of Veterans Affairs
Lafayette Building
811 Vermont Street, NW Rm 819
Washington, D.C.

Phillip R. Pittman, MD, MPH
COL, MC, USA
Chief, Division of Medicine
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7 April 2005

Slide adapted from: Pittman PR. Studies on the Health Effects of Multiple Vaccines: Completed and Ongoing. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Apr 7, 2005; Washington, DC.

Hyper Immunization

- **Studies have been done to assess the long-term medical risk of repeated injections with multiple antigens at Fort Detrick for many years.**
- **In the 1950s Fort Detrick had a group of workers who had received repeated injections with multiple antigens of bacterial, rickettsial and viral origins.**

Slide adapted from: Pittman PR. Studies on the Health Effects of Multiple Vaccines: Completed and Ongoing. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Apr 7, 2005; Washington, DC.

What are the Fort Detrick Vaccine Safety Studies

- **1958 - Peeler RN, Cluff LE, Trever RW. Hyper-immunization of man. *Bulletin of the Johns Hopkins Hospital* 1958;103:183-98.**
- **1965 - Peeler RN, Kadull PJ, Cluff LE. Intensive immunization of man: Evaluation of possible adverse consequences. *Annals of Internal Medicine* 1965;63:44-57.**
- **1974 - White CS III, Adler WH, McGann VG. Repeated immunization: Possible adverse effects: Reevaluation of human subjects at 25 years. *Annals of Internal Medicine* 1974;81:594-600.**

Slide adapted from: Pittman PR. Studies on the Health Effects of Multiple Vaccines: Completed and Ongoing. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Apr 7, 2005; Washington, DC.

Study 3 : 25-year follow-up 1971: Conclusion

- **"These data and the accompanying evaluation of an intensively immunized population provide evidence that no obvious adverse effects result from repeated immunization."**
- **There are some laboratory mean values that are different but the means often were within the normal range and do not support a clinical illness.**
- **There were no disease or clinical symptom complex found related to multiple immunization in either studies over a 25 year period.**

Slide adapted from: Pittman PR. Studies on the Health Effects of Multiple Vaccines: Completed and Ongoing. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Apr 7, 2005; Washington, DC.

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Long-term health effects of repeated exposure to multiple vaccines☆

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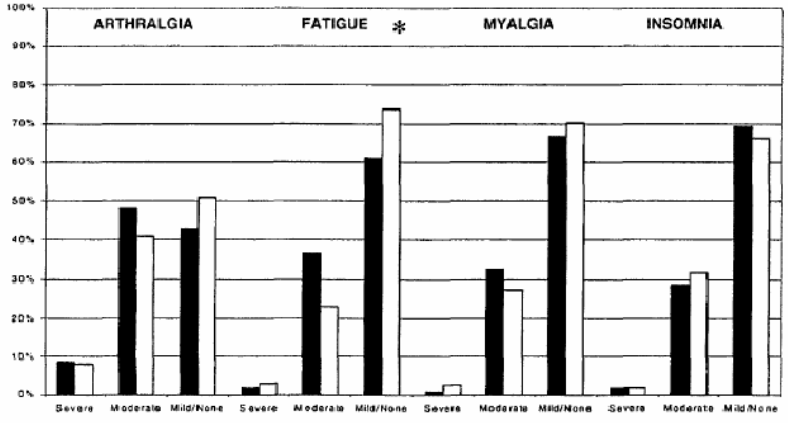
Received 14 January 2004; received in revised form 6 May 2004; accepted 4 June 2004
Available online 23 July 2004

Slide adapted from: Pittman PR. Studies on the Health Effects of Multiple Vaccines: Completed and Ongoing. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Apr 7, 2005; Washington, DC.

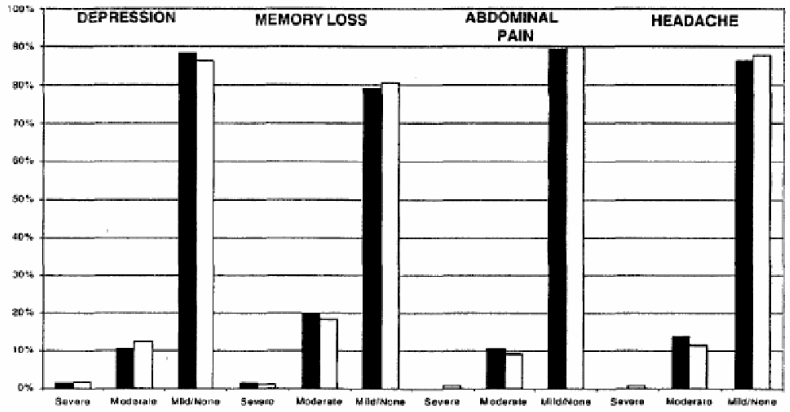
Long-term health effects?

- **The health of 155 former workers in a US military research program who had received multiple vaccines and 265 matched community controls was assessed.**
- **The vast majority of the study group were recruited and enrolled during a biannual alumni meeting in 1996 at Fort Detrick, MD.**
- **Controls were recruited from among age, race, gender matched community controls within Frederick county.**

Slide adapted from: Pittman PR. Studies on the Health Effects of Multiple Vaccines: Completed and Ongoing. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Apr 7, 2005; Washington, DC.



Slide adapted from: Pittman PR. Studies on the Health Effects of Multiple Vaccines: Completed and Ongoing. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Apr 7, 2005; Washington, DC.



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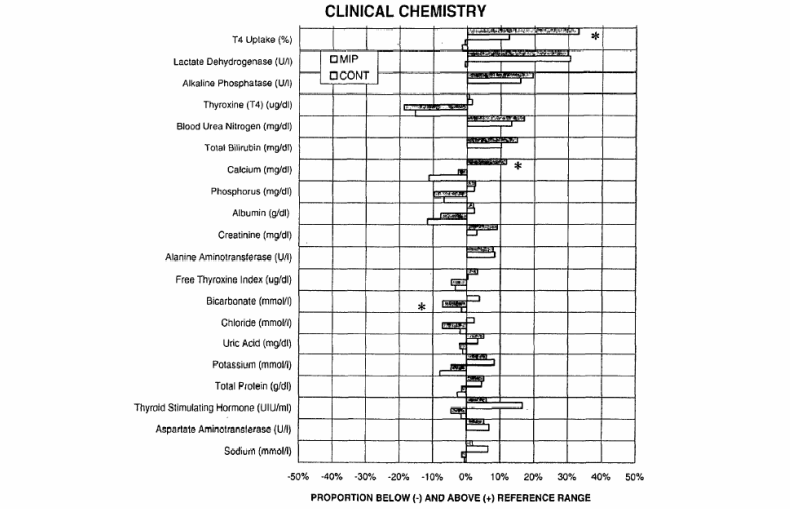

Fig. 2. Comparison of abnormal serum chemistry values for MIP (dark-colored bars) and control (light-colored bars) subjects. The proportions of each group with values above and below the laboratory reference range for each test are displayed as positive and negative, respectively. Asterisk denotes test for which a statistically significant difference between MIP and control subjects was seen (one-tailed *P*-value adjusted for multiple comparisons).

Slide adapted from: Pittman PR. Studies on the Health Effects of Multiple Vaccines: Completed and Ongoing. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Apr 7, 2005; Washington, DC.

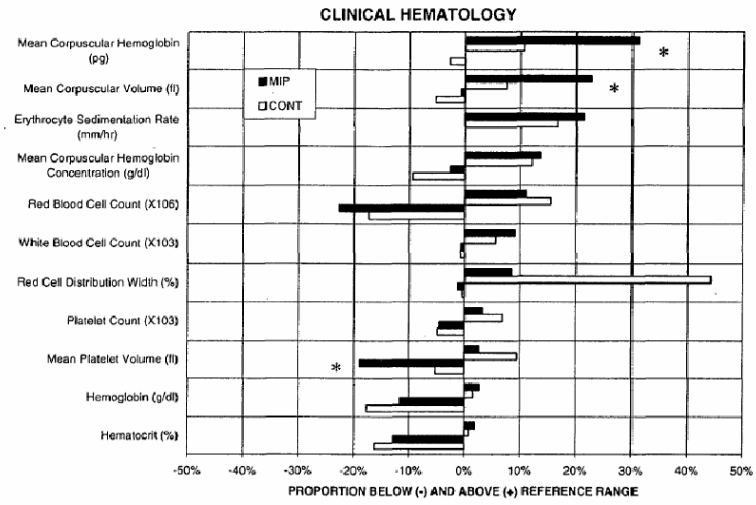

Fig. 3. Comparison of abnormal clinical hematology values for MIP (dark-colored bars) and control (light-colored bars) subjects. The proportions of each group with values above and below the laboratory reference range for each test are displayed as positive and negative, respectively. Asterisk denotes test for which a statistically significant difference between MIP and control subjects was seen (one-tailed P-value adjusted for multiple comparisons).

Slide adapted from: Pittman PR. Studies on the Health Effects of Multiple Vaccines: Completed and Ongoing. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Apr 7, 2005; Washington, DC.

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Journal of Immunological Methods 286 (2004) 47–67

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Research Paper

Detection of antibodies to squalene III. Naturally occurring antibodies to squalene in humans and mice☆

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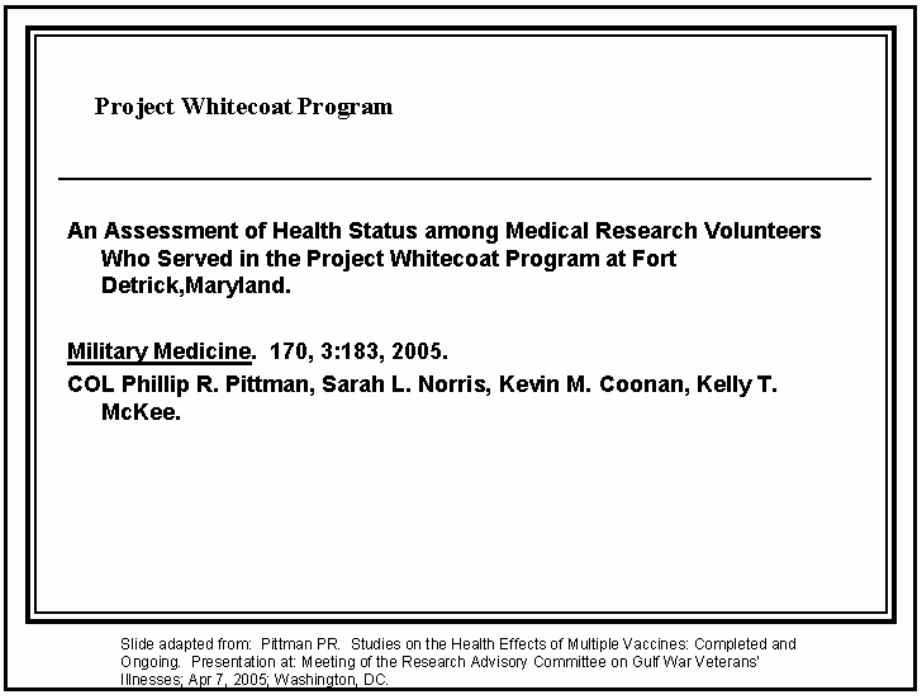
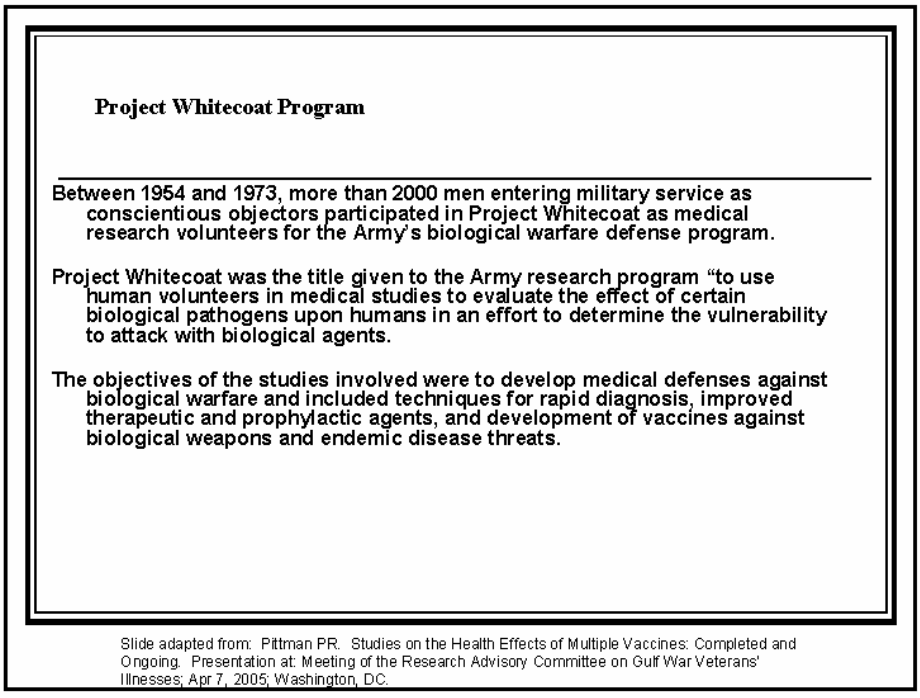
Received 26 August 2003; received in revised form 7 November 2003; accepted 11 November 2003

Slide adapted from: Pittman PR. Studies on the Health Effects of Multiple Vaccines: Completed and Ongoing. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Apr 7, 2005; Washington, DC.


Project Whitecoat Program
An Assessment of Health Status among Medical Research Volunteers Who Served in the Project Whitecoat Program at Fort Detrick,Maryland.
Military Medicine. 170, 3:183, 2005.
COL Phillip R. Pittman, Sarah L. Norris, Kevin M. Coonan, Kelly T. McKee.
Slide adapted from: Pittman PR. Studies on the Health Effects of Multiple Vaccines: Completed and Ongoing. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Apr 7, 2005; Washington, DC.


Project Whitecoat Program
Between 1954 and 1973, more than 2000 men entering military service as conscientious objectors participated in Project Whitecoat as medical research volunteers for the Army's biological warfare defense program.
Project Whitecoat was the title given to the Army research program "to use human volunteers in medical studies to evaluate the effect of certain biological pathogens upon humans in an effort to determine the vulnerability to attack with biological agents.
The objectives of the studies involved were to develop medical defenses against biological warfare and included techniques for rapid diagnosis, improved therapeutic and prophylactic agents, and development of vaccines against biological weapons and endemic disease threats.
Slide adapted from: Pittman PR. Studies on the Health Effects of Multiple Vaccines: Completed and Ongoing. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Apr 7, 2005; Washington, DC.

Project Whitecoat Program

The group participated in more than 135 clinical research studies involving exposure to live agents, receipt of investigational vaccines, and studies of metabolic and psychological effects of environmental-and infection-induced stress.

This study was designed to assess the long-term effects on health of these men resulting from their involvement in this vital program.

Slide adapted from: Pittman PR. Studies on the Health Effects of Multiple Vaccines: Completed and Ongoing. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Apr 7, 2005; Washington, DC.

EXPOSURES

- 358 volunteers "Exposed" (received study product) to:
  - Investigational vaccines: 197
  - Disease-causing agents: 211
  - Antibiotics/other therapeutic agents: 46
- 164 "Controls" (did not receive study product)

Slide adapted from: Pittman PR. Studies on the Health Effects of Multiple Vaccines: Completed and Ongoing. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Apr 7, 2005; Washington, DC.

VACCINE EXPOSURES

- VEE: 73
- Tularemia: 45
- Yellow Fever: 31
- EEE: 29
- WEE: 28
- Plague: 13
- Q-fever: 11
- Rift Valley fever: 8
- Anthrax: 7
- Chikungunya: 6
- Adenovirus: 4

Slide adapted from: Pittman PR. Studies on the Health Effects of Multiple Vaccines: Completed and Ongoing. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Apr 7, 2005; Washington, DC.

DISEASE AGENT EXPOSURES

- *Coxiella burnetii* (Q-fever): 58
- Sandfly fever: 30
- Staphylococcal enterotoxin B (SEB): 20
- *Francisella tularensis* (tularemia): 11
- Venezuelan equine encephalitis (VEE): 7
- *Pseudomonas* endotoxin: 2

Slide adapted from: Pittman PR. Studies on the Health Effects of Multiple Vaccines: Completed and Ongoing. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Apr 7, 2005; Washington, DC.

Whitecoat Project

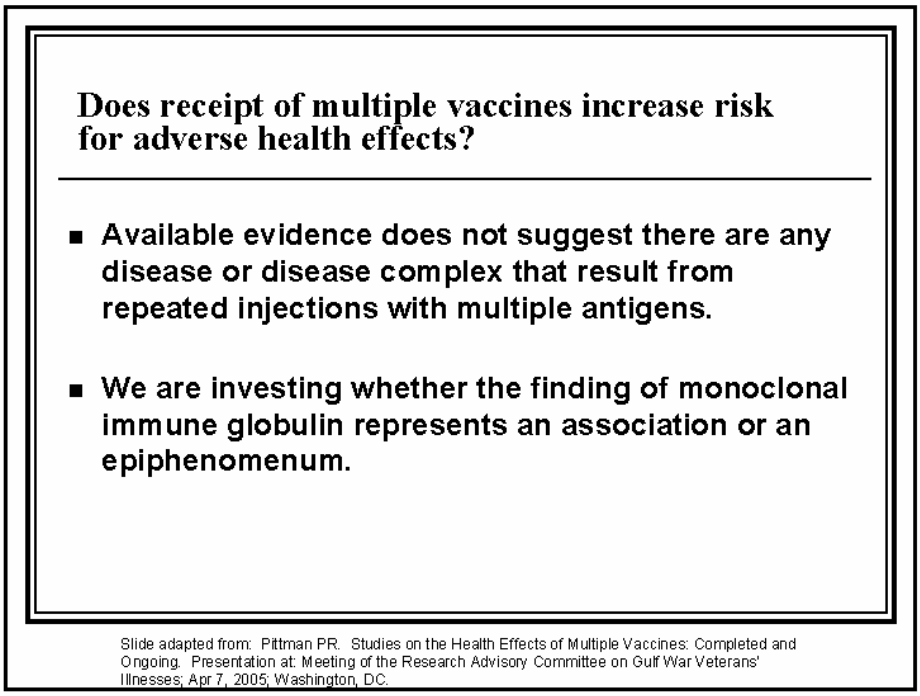
- Asthma reported more frequently among tularemia vaccine recipients than controls (13.3% vs 2.4%, p=0.049)
- Asthma reported more frequently in group exposed to non-agents than controls (13.0% vs 2.4%, p=0.050)
- No definite association

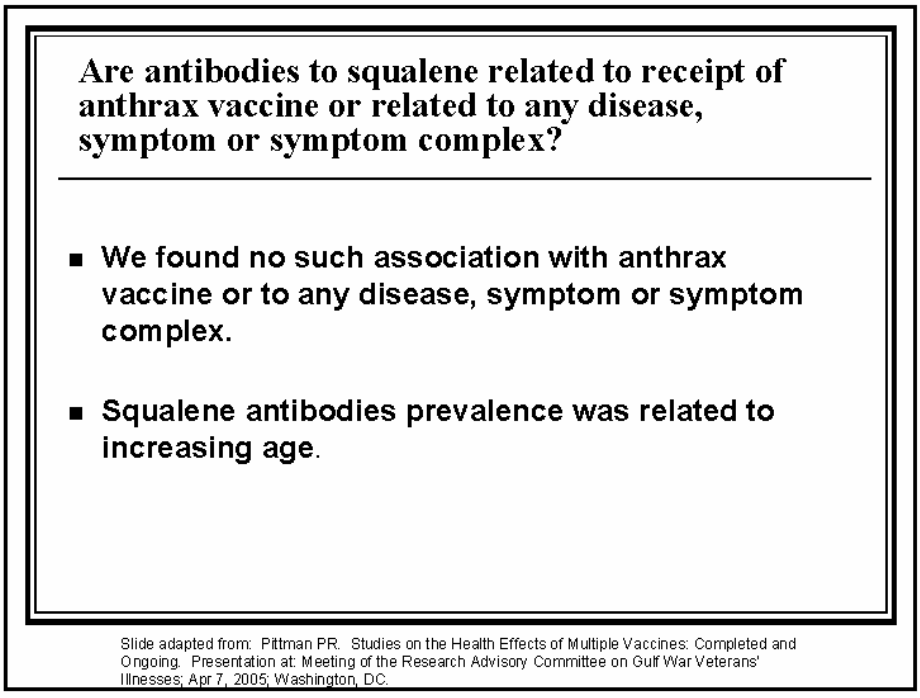
Slide adapted from: Pittman PR. Studies on the Health Effects of Multiple Vaccines: Completed and Ongoing. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Apr 7, 2005; Washington, DC.

CONCLUSIONS (CONT)

- No significant differences between "exposed" and "unexposed" subjects with regard to self-reported diseases or medical conditions
- No differences between individuals participating in one and those participating in two or more studies with regard to any outcome measured (general health, exercise level, children, symptoms, or medical conditions)

Slide adapted from: Pittman PR. Studies on the Health Effects of Multiple Vaccines: Completed and Ongoing. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Apr 7, 2005; Washington, DC.


Does receipt of multiple vaccines increase risk for adverse health effects?
Available evidence does not suggest there are any disease or disease complex that result from repeated injections with multiple antigens.
We are investing whether the finding of monoclonal immune globulin represents an association or an epiphenomenum.
Slide adapted from: Pittman PR. Studies on the Health Effects of Multiple Vaccines: Completed and Ongoing. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Apr 7, 2005; Washington, DC.


Are antibodies to squalene related to receipt of anthrax vaccine or related to any disease, symptom or symptom complex?
We found no such association with anthrax vaccine or to any disease, symptom or symptom complex.
Squalene antibodies prevalence was related to increasing age.
Slide adapted from: Pittman PR. Studies on the Health Effects of Multiple Vaccines: Completed and Ongoing. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Apr 7, 2005; Washington, DC.

CONCLUSION

- Vaccines, including multiple vaccine antigen injections, appear to have a safe long-term health outcome.

Slide adapted from: Pittman PR. Studies on the Health Effects of Multiple Vaccines: Completed and Ongoing. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Apr 7, 2005; Washington, DC.

Animal Studies: Effects of Vaccines

Vaccines

★☆★ RAC-GWVI

Assessment of a role of stress-activated kinases in the pathogenesis of Gulf War Syndrome

Ya Fang Liu M.D. & Ph.D.
Department of Pharmacology
Boston University School of Medicine

Slide adapted from: Liu YF. Assessment of a Role of Stress-activated Kinasas in the Pathogenesis of Gulf War Syndrome. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Feb 23, 2005; Washington, DC.

Stress-activated kinases

They are a group of enzymes or kinases that are activated in response to stressful stimuli such as UV light, γ–irradiation, inflammatory cytokines, certain chemicals, toxins.

Activation of these kinases indicates that cells or neurons are undergoing cellular stress.

Slide adapted from: Liu YF. Assessment of a Role of Stress-activated Kinasas in the Pathogenesis of Gulf War Syndrome. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Feb 23, 2005; Washington, DC.

Pathological role of stress-activated kinases

Over-activation of stress-activated kinases can induce dysfunction of central nervous and immune systems.

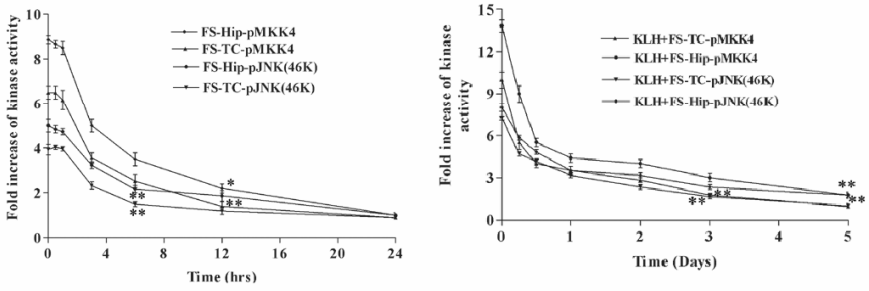
Slide adapted from: Liu YF. Assessment of a Role of Stress-activated Kinasas in the Pathogenesis of Gulf War Syndrome. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Feb 23, 2005; Washington, DC.

Hypothesis

Stress, vaccination, and exposure to one or more chemicals may synergistically act on stress-activated kinases. Over-activation of these stress-activated kinases may lead to dysfunction in the central nervous and immune systems, contributing the majority of symptoms observed in patients with GWS

Slide adapted from: Liu YF. Assessment of a Role of Stress-activated Kinasas in the Pathogenesis of Gulf War Syndrome. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Feb 23, 2005; Washington, DC.

KLH significantly prolongs activation of MKK4 in the brain



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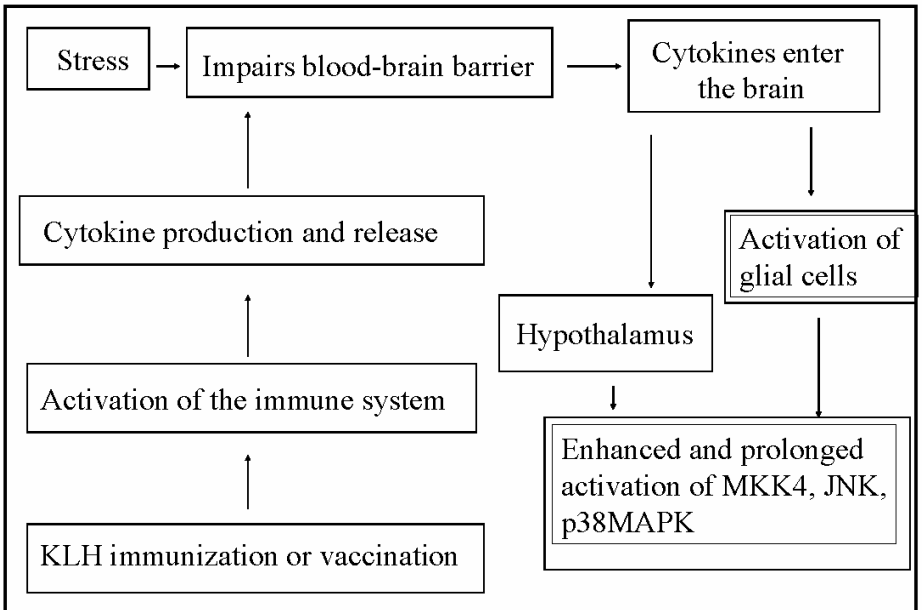

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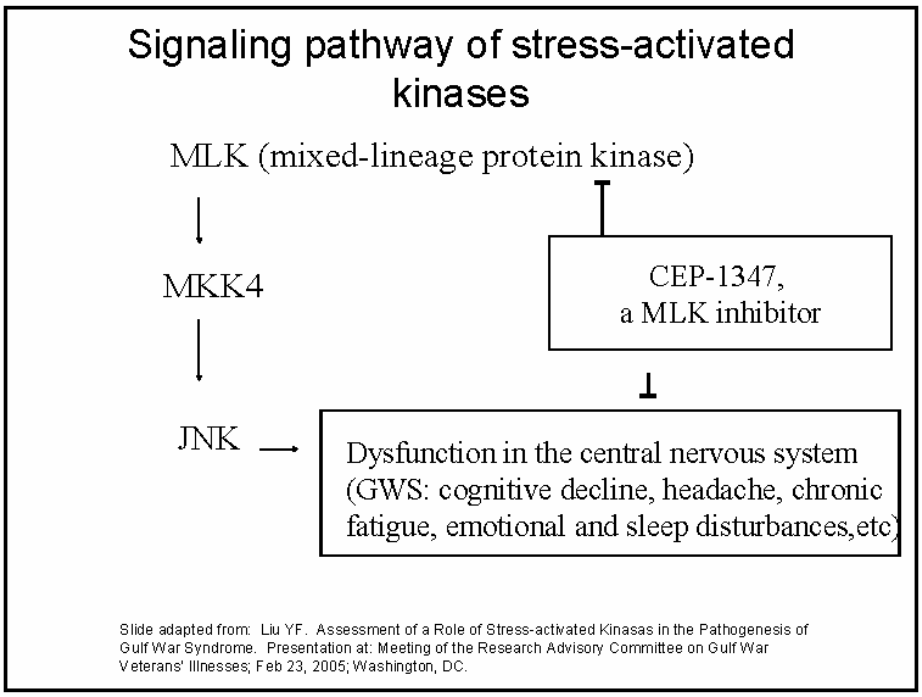
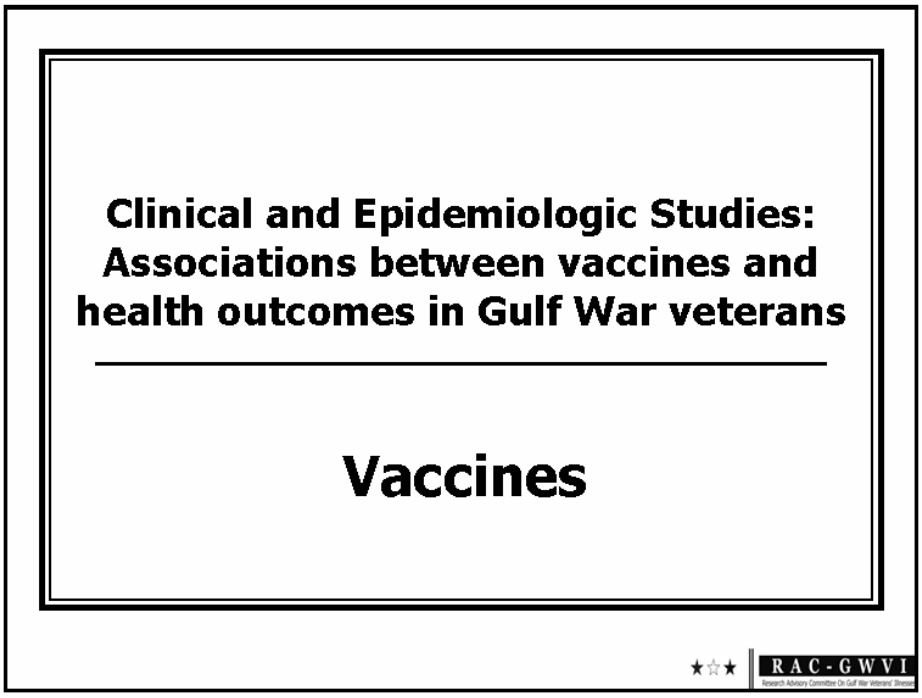

Signaling pathway of stress-activated kinases
MLK (mixed-lineage protein kinase)
MKK4
JNK
CEP-1347, a MLK inhibitor
Dysfunction in the central nervous system (GWS: cognitive decline, headache, chronic fatigue, emotional and sleep disturbances,etc)
Slide adapted from: Liu YF. Assessment of a Role of Stress-activated Kinasas in the Pathogenesis of Gulf War Syndrome. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Feb 23, 2005; Washington, DC.


Clinical and Epidemiologic Studies: Associations between vaccines and health outcomes in Gulf War veterans
Vaccines
RAC-GWVI

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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Slide adapted from: Mahan CM. Anthrax Vaccination and Self-reported Symptoms, Functional Status and Medical Conditions in the National Health Survey of Gulf War Era Veterans and Their Families. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Oct 28, 2003; Washington, DC.

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

Slide adapted from: Mahan CM. Anthrax Vaccination and Self-reported Symptoms, Functional Status and Medical Conditions in the National Health Survey of Gulf War Era Veterans and Their Families. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Oct 28, 2003; Washington, DC.

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=3861)	No (N=2979)	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(1.08-2.10)
Runny nose	21.7	17.8	12.9	20.5	1.53 (1.33-1.76)	1.43 (1.24-1.64)	1.32(0.98-1.81)
Headaches	21.4	17.7	11.3	16.8	1.69 (1.46-1.95)	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)	1.33(0.93-1.91)
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 (15) 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).

Slide adapted from: Mahan CM. Anthrax Vaccination and Self-reported Symptoms, Functional Status and Medical Conditions in the National Health Survey of Gulf War Era Veterans and Their Families. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Oct 28, 2003; Washington, DC.

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)

Slide adapted from: Mahan CM. Anthrax Vaccination and Self-reported Symptoms, Functional Status and Medical Conditions in the National Health Survey of Gulf War Era Veterans and Their Families. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Oct 28, 2003; Washington, DC.

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.

Slide adapted from: Mahan CM. Anthrax Vaccination and Self-reported Symptoms, Functional Status and Medical Conditions in the National Health Survey of Gulf War Era Veterans and Their Families. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Oct 28, 2003; Washington, DC.

Vaccines and Gulf War Illnesses:

Squalene Antibodies in Ill Gulf War Veterans?

Asa, Cao, Garry (2000)

	ASA assay positive
Blinded sample	
PGW sick (n=38)	95 %
PGW, well (n=12)	0 %
Nondepl Gulf era (n=6)	100 %
Unblinded sample	
Gulf veterans (n=86)	69%
Blood bank donors (n=48)	5%

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Squalene Antibodies in Post-Gulf AVA Recipients?

Asa, Wilson, Garry (2002)

	Symps?	ASA positive
Pilot: 6 AVIP with GWI-like symps	all (by def)	100%
Blinded sample		
19 healthy nonmilitary (age/sex matched)	0 (by def)	16%
25 AVIP vaccine recipients	52%	32%
- 17 got AVA from 5 lots	76%	47%
- 8 got AVA from other lots	0%	0%

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Additional information on Anthrax Vaccine

- Anthrax vaccine is among the most reactogenic vaccines in the VAERS
- Adverse effects related to number of doses
- Receipt of anthrax vaccine consistently related to chronic ill health in epidemiologic studies of Gulf War veterans
- Adverse effects generally found to be higher in female than male AVA recipients
- Pertussis (UK adjuvant for AVA) used experimentally to generate autoimmune disease in animals

Slide adapted from: Golomb BA. Vaccinations and Illness in Persian Gulf Veterans. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Apr 7, 2005; Washington, DC.

Epidemiologic Studies: Association of Individual Vaccines with Health of Gulf Veterans

Study	Outcome	Vaccine	Findings
Boyd, 2003 (973 Gulf vets in Registry)	High vs. low # of symptoms	Botulinum Anthrax Meningococcus Others	OR = 1.78* OR = 1.72* OR = 1.57 NS
Canadian MOD (3,113 Gulf vets)	Chronic fatigue Cogn dysf	"nonroutine" (anthrax, plague)	OR = 1.92* OR = 1.28*
Gray, 2002 (3.831 PGW vets)	GWI case def	Meningococcus Botulinum Anthrax Plague Typhoid	OR = 3.64* (unadj); 1.30*(adj) OR = 4.92* (unadj); 1.28 (adj) OR = 3.72* (unadj); 1.01 (adj) OR = 3.23* (unadj); 0.94 (adj) OR = 2.34* (unadj); 0.93 (adj)
Wolfe, 2002 (1290 Gulf vets)	CMI	Anthrax	OR = 1.5* (adj)
Unwin, 1999 (2,735 Gulf vets)	CMI	Anthrax Plague Tetanus Any biological Other	OR = 1.5* OR = 1.3* OR = 1.3* OR = 1.5* NS

* Indicates statistical significance, p<0.05

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Association of Multiple Vaccines with Health of Gulf Veterans

Study	Outcome	Vaccine	Findings
Cherry, 2001 (8,210 Gulf vets)	Symptom severity score		All* / Periph*
		0	2.0 / -26.4
		1-3	2.8 / -2.7
		4-6	3.5 / 8.2
		7-9	4.2 / 23.6
		10+	4.5* / 34.4
Hotopf (923 Gulf vets w/shot records)	CMI	Postdeployment	
		0/1	OR = 1.0
		2	OR = 2.2*
		3	OR = 2.4*
		4	OR = 2.2*
		5+	OR = 5.0*
Australian study (1,426 Australian vets, used shot records)	# of symptoms	0	Ratio of means = 1.0
		1-4	RM = 0.9
		5-9	RM = 1.0
		10+	RM = 1.3*

* Indicates statistical significance, p<0.05

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Vaccines:
Information Considered by RAC in 2004-2005

- Vaccine exposure/adverse effects
- Clinical/Epidemiologic studies

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Vaccines: Summary of Information Considered

Vaccine Exposures/Adverse Effects

- Multiple vaccines given to GW veterans; most concern raised about AVA, effects of multiple vaccines
- Changes in AVA manufacturing process around the time of the Gulf War, concerns about quality control/contamination in early 1990s. Current AVA may not be comparable to 1990 AVA
- AVA has now been given to >1 million U.S. military; multiple studies suggest minimal long-term concerns re: VAERS claims, hospitalization, disability claims

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Vaccines: Summary of Information Considered

Vaccine Exposures/Adverse Effects

- USAMRID studies indicate that intensive receipt of multiple vaccinations, in general, not associated with chronic health problems; limitations in generalizability of these findings
- No systematic evaluation of chronic symptom complexes similar to those seen in Gulf war veterans with respect to:
  - *AVA; specifically 1990-1991 AVA*
  - *Multiple vaccinations associated with 1990-1991 Gulf War*

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Vaccines: Summary of Information Considered

Clinical and Epidemiologic Studies

- Epidemiologic studies consistently identify sign. associations between individual vaccines and chronic ill health in Gulf War veterans
  - *Anthrax: ORs ~ 1.3 – 3.7*
  - *Botulinum toxoid: ORs ~1.8 – 4.9*
  - *Meningococcus: ORs ~1.6 – 3.6*
- Epidemiologic studies also support associations between increased number of vaccines and chronic ill health in Gulf War veterans
- Important to consider reporting bias in studies relying on self-reported receipt of vaccines

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Vaccines: Summary of Information Considered

Clinical and Epidemiologic Studies: Squalene

- Asa et al report association between chronic symptoms and presence of antibodies to squalene in ill Gulf War veterans and recipients of AVA in AFIP
- USAMRID studies suggest squalene antibodies naturally occur in the general population, increase with age
- Additional ongoing Army study is assessing presence/absence of squalene antibodies in ill/healthy Gulf War veterans

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Unanswered Questions re: Vaccines and the Health of Gulf War Veterans

- Anthrax or other Gulf War-era vaccines associated with long-term symptom complexes similar to those reported by Gulf War veterans?
- Adverse effects of Gulf War-era vaccines in nondeployed military personnel?
- Little information on GW veterans' health in relation to specific vaccine combinations
- No evaluation of vaccine-related risk in Gulf War subgroups (e.g. by branch, unit, lot)
- Possible interaction of vaccines with other Gulf War exposures?

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Vaccines and Gulf War Illnesses: Unanswered Questions Related to Squalene

- Anti-squalene antibodies in Gulf War veterans?
  - Do veterans with Gulf War illnesses have an elevated level of antibodies to squalene (whether or not in relation to AVA)?
  - If so, is their presence a marker for and/or a cause of GWI?
- Was squalene in vaccines used during the Gulf War?
  - Used as an adjuvant to enhance vaccine immunogenicity?
  - In vaccines for some other reason (e.g., contaminant)?
  - Levels capable of causing chronic illness?

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Discussion of Recommendations

Animal/Toxicological Research:
- *Neuro, immune effects of combinations of vaccines; vaccines in combination with other exposures?*

Epidemiologic Studies: studies should focus on 1991 vaccines
- Blinded case/control evaluation of squalene antibodies in ill/healthy Gulf veterans using ASA and Army assays
- Identify Gulf veteran subgroups known to have received AVA, compare health parameters to group that didn't
- Epi evaluations of other individual and combinations of Gulf War-era vaccines among veterans who have shot records

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Presentation 5 – Lea Steele

Infectious Diseases

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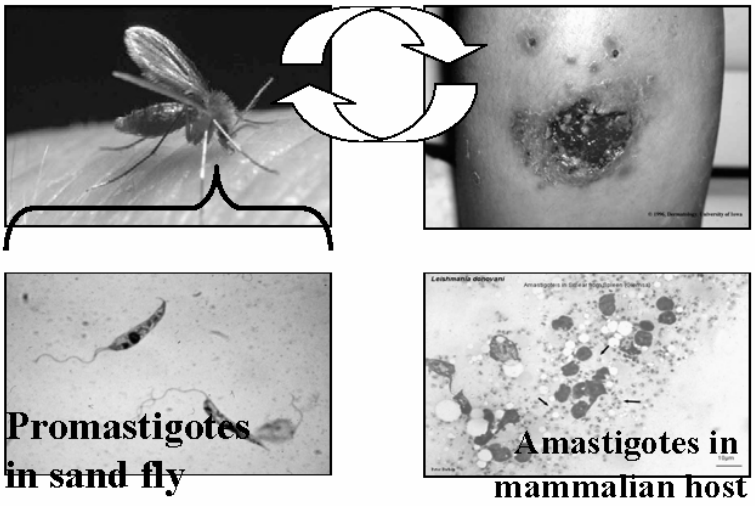
Leishmaniasis in Veterans of Desert Storm & Iraqi Freedom

Alan J. Magill MD, FACP
Science Director
Walter Reed Army Institute of Research

Slide adapted from: Magill AJ. Leishmaniasis in Veterans of Desert Storm & Iraqi Freedom. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; February 23, 2004; Washington, DC.

Leishmania Parasite Life Cycle



Slide adapted from: Magill AJ. Leishmaniasis in Veterans of Desert Storm & Iraqi Freedom. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; February 23, 2004; Washington, DC.

Leishmania infection and 1990-91 Gulf War

- **What else did we see?**
- **Atypical "viscerotropic leishmaniasis"**
  - **– *L. tropica* parasites**
  - **– Desert rodent or human reservoir??**
  - **– Sand fly vector?**
- **N = 12 cases, parasitologically confirmed**
- **N = ?? cases total**

Slide adapted from: Magill AJ. Leishmaniasis in Veterans of Desert Storm & Iraqi Freedom. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; February 23, 2004; Washington, DC.

What was unusual?

- **Did not expect to see VL in Saudi Arabia**
- **Atypical, non-specific clinical syndrome**
  - **Not typical Visceral Leishmaniasis**
  - **Smear negative, culture positive**
- **Isolation of *Leishmania* from bone marrow**
- **Characterization of isolates as *L. tropica***
- **Difficult diagnosis, insensitive tests**

Slide adapted from: Magill AJ. Leishmaniasis in Veterans of Desert Storm & Iraqi Freedom. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; February 23, 2004; Washington, DC.

NEJM. May 13, 1993

Table 1. Clinical Presentation of Eight Male Patients with Visceral Leishmaniasis, at the Time of Confirmatory Culture.

Patient No.	Incubation Period (Mo)	Signs and Symptoms at Presentation	Fever	Abdominal Pain*	Malaise*	Fatigue*	Physical Examination
1	2	Adenopathy	Yes	++	+	++	Hepatomegaly, splenomegaly, adenopathy
2	1–4	Fever	Yes	+	++	+	Normal findings
3	2–8	Gastroenteritis	No	+++	+++	+	Splenomegaly
4	2–6	None	No	No	No	No	Normal findings
5	4–12	Chronic fatigue with hepato-splenomegaly	Yes	+	+	+++	Hepatomegaly, splenomegaly
6	7–14	Chronic fatigue with adenopathy	No	+	+	+++	Hepatomegaly, adenopathy
7	1–6	Mononucleosis	Yes	+/−	+++	+	Normal findings
8	3–12	Fever of unknown origin	Yes	+	++	++	Hepatomegaly, splenomegaly

*One plus sign indicates that the patient reported the symptom when questioned by the examiner; two plus signs, that the patient himself reported the symptom without questioning; and three plus signs, that the symptom was the primary one. Patient 7, represented by the plus–minus sign, reported abdominal pain of brief duration associated with diarrhea.

Slide adapted from: Magill AJ. Leishmaniasis in Veterans of Desert Storm & Iraqi Freedom. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; February 23, 2004; Washington, DC.

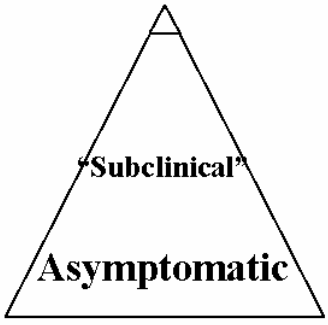
Leishmania in 1st Gulf War

- Characterizations of *L. tropica* based on CAE of 21 enzymes
- 3 clusters of *L. tropica*
- *Am J Trop Med Hyg. 1993. 49:357*

Slide adapted from: Magill AJ. Leishmaniasis in Veterans of Desert Storm & Iraqi Freedom. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; February 23, 2004; Washington, DC.

Visceral Leishmaniasis Disease Spectrum

1-3% with overt VL



- "Subclinical" Syndromes
  - Chronic systemic illness
  - Acute febrile illness
- Risk factors for progression
  - Malnutrition
  - Immunosuppression (AIDS)
  - Genetic?
- Cause of death
  - Measles
  - Pneumonia
  - TB
  - dysentery

Slide adapted from: Magill AJ. Leishmaniasis in Veterans of Desert Storm & Iraqi Freedom. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; February 23, 2004; Washington, DC.

Can Cytokines Cause Disease?

- **Chronic disease**
  - Fever, malaise, myalgias, arthralgias, fatigue, anorexia, nausea
  - Inflammatory bowel disease, rheumatoid arthritis,
  - TNFα, INFγ, IL-2, IL-12, etc.

Slide adapted from: Magill AJ. Leishmaniasis in Veterans of Desert Storm & Iraqi Freedom. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; February 23, 2004; Washington, DC.

Persistent *Leishmania* Infection

- **Intracellular pathogen of the macrophage**
- **Lifelong, persistent infection**
- **Treat disease, never eradicate parasites**
- **Mycobacteria: TB, leprosy**
- **Bacteria: *Brucella***
- **Fungal: *Histoplasma***
- **Viral: *HIV***

Slide adapted from: Magill AJ. Leishmaniasis in Veterans of Desert Storm & Iraqi Freedom. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; February 23, 2004; Washington, DC.

Research on Infectious Diseases in Gulf War Veterans

Assessments of Infectious Diseases in CDC Study of Gulf veterans in PA Air National Guard
(Fukuda et al, JAMA1998 280:981-8)

- 99 GW multisymptom illness cases veterans vs. 59 GW controls
- Evaluated: Stool specimens for multiple organisms
  Serologic (antibody) testing for multiple organisms
- Stool specimens: no salmonella, shigella, campylobacter, yersinia, e.coli, microsporidia, cryptosporidium, cyclospora
- Serology: no antibodies to West Nile, Toscana, Karimbad, Isfahan, shistosomiasis species

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Research on Infectious Diseases in Gulf War Veterans

	Stool Specimen Testing
Blastocystis hominis	7% cases, 12% controls
Giardia	1% of mild cases, 2% of controls
Enteroviruses	9% of mild cases, 10% of controls
	Serologic Testing
Yellow fever	83% positive (due to vaccine), no diff by case
Botulinum toxin	6% positive, no difference by case status
Anthrax PA	9% positive, no difference by case status
Leishmania	5% positive; no difference by case status
Toxoplasma gondii	19% positive, no difference by case status
Dengue fever	10% positive, no difference by case status
Sand fly fever	9% cases, 2% controls

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Research on Infectious Diseases in Gulf War Veterans

Human Herpesviruses (Wallace et al, Clin Diag Lab Imm 1999 6:216-223)

- 46 Gulf veterans who met criteria for chronic fatigue syndrome vs. 32 in good health
- Evaluated: Antibody titers to HHV6 and EBV
  PCR for HHV6, HHV7, EBV, CMV in periph mono cells
- Found no differences by serology or PCR between sick and healthy veterans
- Gulf veterans, overall, had lower prevalence of herpes virus DNA than civilians

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Research on Infectious Diseases in Gulf War Veterans

Cellular and Humoral Immune Abnormalities in Gulf War Veterans (Vojdani et al, Env Health Perspect 2004 112:840-846)

- 100 symptomatic Gulf veterans in clinical lab sample, compared to 50 asymptomatic nondeployed Army and 50 civilian controls (age/sex matched)
- Symptomatic Gulf veterans had significantly elevated mean antibody titers of:
  - *EBV IgM (VCA)*
  - *CMV IgG*
  - *HSV-1 IgG*
  - *HSV-2 IgG*
  - *HHV-6 IgG*
  - *VZV IgG*

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Research on Infectious Diseases in Gulf War Veterans

Prevalence of *Leishmania tropica* in a random sample of 200 Gulf War veterans
(D Bourdette, M Riscoe, R Houghton, S Reed et al, unpublished)

- First 200 subjects in population-based study tested for reactivity to *L.tropica* recombinant protein using an ELISA test.
- Samples considered positive if values > 3 SDs above the mean value in a population of healthy, nonveteran controls
- Positive serology found in 18 (9%) veterans; none had evidence of clinically active leishmaniasis

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Research on Infectious Diseases in Gulf War Veterans

Leishmania tropica and GWI case/control status

- 110 Gulf veteran GWI cases; 57 controls
  (cases: 1 or more of musculoskeletal pain, cognitive problems, gastrointestinal problems, skin lesions, fatigue)
- Antibody positive: 10% cases, 4% controls (exact p value = 0.149)
- Remaining subjects not assessed, findings not followed-up
- Sensitivity/specificity of test not known

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Research on Infectious Diseases in Gulf War Veterans

Mycoplasma infection

- *Mycoplasma* organisms lack a cell wall, capable of independent self-replication
- *Mycoplasma* species are associated with human diseases affecting a variety of organ systems (e.g., *m. pneumoniae, m. genitalium, m. hominis*). They can be present without causing illness or can cause chronic infections, and can be particularly aggressive in immunocompromised patients

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Research on Infectious Diseases in Gulf War Veterans

Mycoplasma infection in Gulf veterans

- Dr. Garth Nicolson first reported high infection rate by *mycoplasma fermentans* in ill Gulf veterans and family members; detection required specialized PCR methods
- He also reported these infections and multisymptom illness can be treated successfully with multiple extended courses of doxycycline, other antibiotics

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Research on Infectious Diseases in Gulf War Veterans

Mycoplasma infection in Gulf veterans

- Nicolson et al: 45% of symptomatic Gulf veterans test positive for mycoplasma with forensic PCR testing, compared to 9% of controls
- Vojdani et al: 55 % of ill Gulf vets test positive for mycoplasma species (vs. 8 or 15% of healthy controls)
  (also 49% of RA patients, 52% of CFS patients)
- Donta et al: 40% of ill Gulf veterans tested positive for mycoplasma when screened for recruitment into VA's antibiotic treatment trial.

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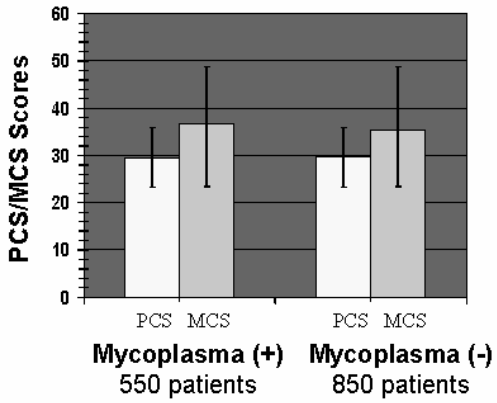
CSP#475 ANTIBIOTIC TREATMENT OF GULF WAR VETERANS' ILLNESSES

Slide adapted from: Donta S. Antibiotic treatment of Gulf War Veterans' Illnesses. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; February 24, 2004; Washington, DC.

Mycoplasma Status and PCS/MCS



Slide adapted from: Donta S. Antibiotic treatment of Gulf War Veterans' Illnesses. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; February 24, 2004; Washington, DC.

Treatment Success (PCS $\geq$ 7 from Baseline) By Rating Period

Rating Period	Doxycycline % Success	Placebo % Success	P-Value
3 Month	21.5	9.9	.001
6 Month	19.7	13.6	.086
9 Month	17.6	14.4	.385
12 Month	18.1	17.3	.905
18 Month	18.2	13.5	.168

Slide adapted from: Donta S. Antibiotic treatment of Gulf War Veterans' Illnesses. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; February 24, 2004; Washington, DC.

ABT: Antibiotic Treatment Trial

491 Gulf War veterans at 26 study sites; 12 mo. doxycycline

	% improved 7 pts. on SF-36	mean SF-36 scores baseline, 12 mos	% mycoplasma neg. @ 18 mos
Doxycycline	**18.0 %**	**30.2 → 32.0**	**90 %**
Placebo	**17.3 %**	**30.1 → 30.9**	**87 %**

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CONCLUSIONS

- Study shows that Doxycycline is an ineffective treatment for GWVI.
- Study casts doubt on the relationship between a persistent mycoplasma infection and GWVI.
- Study documents that patients with GWVI are very ill.

Slide adapted from: Donta S. Antibiotic treatment of Gulf War Veterans' Illnesses. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; February 24, 2004; Washington, DC.

Successful Antibiotic Treatment Of The Gulf War Syndrome A Pilot, Randomized, Placebo Controlled, Blinded Trial

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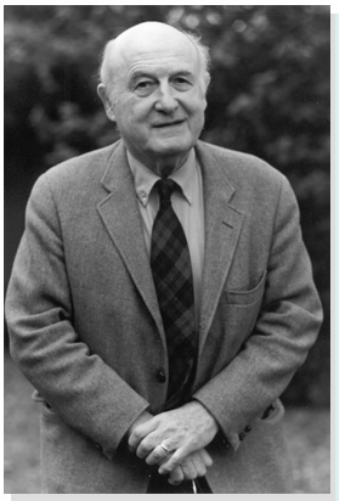
Successful Trial Of Urine Microscopy For Control Of Antibiotic Treatment Of Systemic Coccal Disease

Edward S. Hyman M.D, FACP
William Weiss
and Quentin B. Deming M.D.

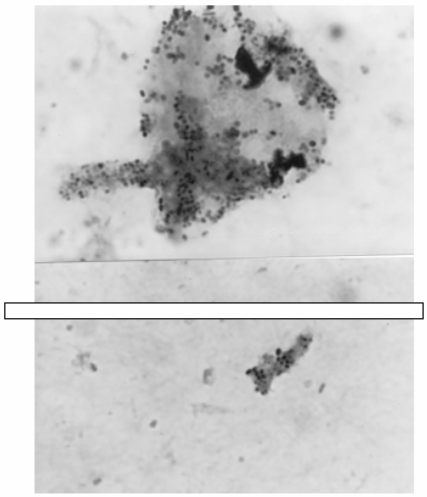
Slide adapted from: Deming QB and Weiss W. Successful Antibiotic Treatment of the Gulf War Syndrome: A Pilot, Randomized, Placebo Controlled, Blinded Trial. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; October 26, 2004; Washington, DC.

Edward S. Hyman M.D, FACP



Slide adapted from: Deming QB and Weiss W. Successful Antibiotic Treatment of the Gulf War Syndrome: A Pilot, Randomized, Placebo Controlled, Blinded Trial. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; October 26, 2004; Washington, DC.

Clusters G+ cocci urine



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Flow Diagram of Protocol

Recruitment & Informed Consent (New Orleans)
!
Pre treatment Evaluation and conformity to admission criteria (SUNY Stony Brook)
!
Randomization (Kunitz & Associates-Maryland)
!
Hospitalized IV Rx, 2-3 weeks (New Orleans) *blinded*
!
oral Rx, 2 months (Home or duty) *blinded*
!
IV Rx, 5 days (New Orleans) *blinded*
!
Oral Rx, 1 mo, (Home or duty) *blinded*
!
Final Evaluation (SUNY Stony Brook) *blinded*
!
KAI breaks code & sends data to statistician

Slide adapted from: Deming QB and Weiss W. Successful Antibiotic Treatment of the Gulf War Syndrome: A Pilot, Randomized, Placebo Controlled, Blinded Trial. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; October 26, 2004; Washington, DC.

Study Cohorts

Evaluable cohort (n=36)

Intent–to–Treat cohort (n=38)

Slide adapted from: Deming QB and Weiss W. Successful Antibiotic Treatment of the Gulf War Syndrome: A Pilot, Randomized, Placebo Controlled, Blinded Trial. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; October 26, 2004; Washington, DC.

Baseline Urine Variables

	Placebo	Treatment	Probability
Protein, %< 2mg/dl	52.9	33.3	0.32
Gram + cocci	29.4	27.8	1.00
Abnormal cocci+	64.7	44.4	0.31
Exploded cocci	82.4	72.2	0.69
Gram - Rods	11.8	11.1	1.0

Slide adapted from: Deming QB and Weiss W. Successful Antibiotic Treatment of the Gulf War Syndrome: A Pilot, Randomized, Placebo Controlled, Blinded Trial. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; October 26, 2004; Washington, DC.

Outcome Variables at Baseline

OUTCOME VARIABLE	PLACEBO	TREATMENT	TOTAL N
Fisk, mean score (ms)	15.1	14.9	36
Fatigue Assessment Index ms)	5.9	5.9	36
Neuropsych impairment index, median score	-0.72*	-0.60	35
Sleep Quality, median score	3.5	3.7	28
Headache, % patients with	88.9	83.3	36
Median number/month	13	18.5	36
Diarrhea, % ≥ 1/day	37.5	25.0	28
Severity score ≥ 3	55.6	33.3	36
Pain, McGill, median score	6.3	6.0	36
Dolorimeter, median score	0.5	1.5	34
Quality of Life, median score	20.0	22.5	36

*one outlier excluded

Slide adapted from: Deming QB and Weiss W. Successful Antibiotic Treatment of the Gulf War Syndrome: A Pilot, Randomized, Placebo Controlled, Blinded Trial. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; October 26, 2004; Washington, DC.

Efficacy Evaluation
Primary Variables

FATIGUE

Modified Fatigue Impact Scale (Fisk)

Baseline	No statistically significant difference
Final (4 months)	p=0.0047
Final from Baseline	p=0.0074

Fatigue Assessment Inventory

Baseline	No statistically significant difference
Final (4 months)	p=0.0005
Final from Baseline	p=0.0002

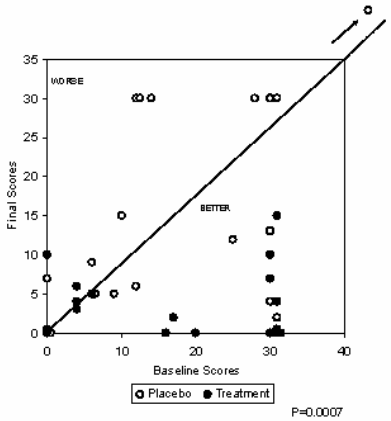
Combined Wilcoxon rank sum test p=0.0007

NEUROPSYCHOLOGICAL IMPAIRMENT INDEX

Baseline	No statistically significant difference
Final (4 months)	No statistically significant difference

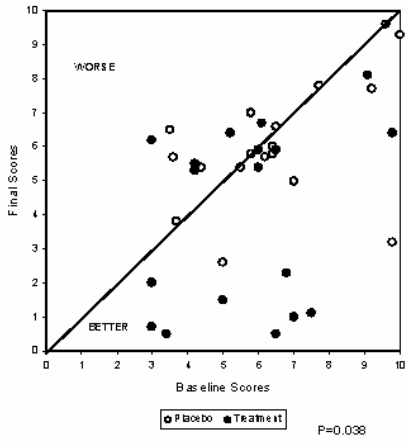
Slide adapted from: Deming QB and Weiss W. Successful Antibiotic Treatment of the Gulf War Syndrome: A Pilot, Randomized, Placebo Controlled, Blinded Trial. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; October 26, 2004; Washington, DC.

Headaches per Month



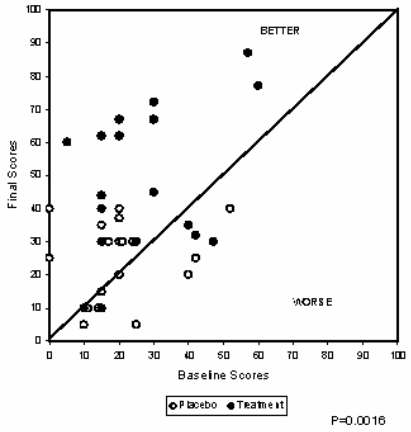
Slide adapted from: Deming QB and Weiss W. Successful Antibiotic Treatment of the Gulf War Syndrome: A Pilot, Randomized, Placebo Controlled, Blinded Trial. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; October 26, 2004; Washington, DC.

Pain: Visual Analog Scale
McGill Scores



Slide adapted from: Deming QB and Weiss W. Successful Antibiotic Treatment of the Gulf War Syndrome: A Pilot, Randomized, Placebo Controlled, Blinded Trial. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; October 26, 2004; Washington, DC.

Quality of Life Scores



Slide adapted from: Deming QB and Weiss W. Successful Antibiotic Treatment of the Gulf War Syndrome: A Pilot, Randomized, Placebo Controlled, Blinded Trial. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; October 26, 2004; Washington, DC.

Conclusions

- A randomized, placebo-controlled, blinded, pilot study has shown that an antibiotic regimen, controlled by monitoring excretion of Gram positive cocci, is effective in ameliorating a syndrome which affects thousands of Gulf War veterans and for which no treatment has previously been proven effective.
- The validity and effectiveness of the urine microscopy method for diagnosis and for control of treatment has been confirmed.
- The hypothesis that Gulf War Syndrome is bacterial in origin, though not proven, is supported.

Slide adapted from: Deming QB and Weiss W. Successful Antibiotic Treatment of the Gulf War Syndrome: A Pilot, Randomized, Placebo Controlled, Blinded Trial. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; October 26, 2004; Washington, DC.

Louisiana study: Summary of Results

	Change from Baseline		
	Placebo	Treated	p value
Fatigue Assessment Inventory Score	+ 3%	+ 36%	<0.001
Fisk Fatigue Impact Scale (pts)	- 1.5	- 6.0	0.007
Headaches per month	- .5	- 16	<0.001
SF-36 score	+ 7	+ 22	0.002
Neuropsych Impairment Index	no change		ns
Sleep quality index score (pts)	+ .2	+ .8	0.06
Diarrhea severity score > 3	- 28%	- 22%	ns
Pain: McGill visual analog	- 0.5	- 0.6	ns

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Infectious Diseases in Gulf War Veterans: What Do We Know?

Leishmania

- "New" presentation of viscerotropic leishmaniasis clinically identified in small number of ill Gulf War veterans; number of undetected cases not known
- Leishmaniasis can be associated with chronic multisymptom illness; no reliable test available
- Pilot study of ELISA test identified leishmaniasis in ~9% of random sample of PGW vets
  - 2nd pilot: potentially higher in symptomatic than nonsymptomatic veterans

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Infectious Diseases in Gulf War Veterans: What Do We Know?

Mycoplasma

- Consistently identified in ~40 % of symptomatic Gulf War veterans (reported in healthy controls @ 8-15%)
- Not clear whether generally associated with Gulf War deployment or nonspecific illness/debilitation

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Infectious Diseases in Gulf War Veterans: What Do We Know?

Other

- Sand fly fever id'd in 9% CMI cases vs. 2% controls in CDC study
- Conflicting results re: herpesviruses
- Little other information re: persistent infections in ill Gulf War veterans
- VA ABT suggested 12 mo. doxycline therapy ineffective; questions re: lab results and study success
- LA study of high-dose, complex antibiotic treatment appears to indicate substantial benefit

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Infectious Diseases in Gulf War Veterans: What Do We Know?

Antibiotic Treatment

- Nicholson case series suggested benefit of 6-wk cycles of antibiotic therapy
- VA ABT suggested 12 mo. doxycline therapy ineffective; questions re: lab results and study success
- LA study of high-dose, complex antibiotic treatment appears to indicate substantial benefit

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Infectious Diseases in Gulf War Veterans: Remaining Questions

- Are any infections associated with GWI?
  - *As a primary cause?*
  - *As cofactors, linked to perpetuation/exacerbation of symptoms?*
  - *As opportunistic infections, resulting from general debilitation?*
- Evaluation and reliable detection of putative infectious agents in Gulf War veterans

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Infectious Diseases in Gulf War Veterans: Remaining Questions

- Does antibiotic treatment improve GWI symptoms?
  - ***Potentially by eliminating specific types of infection or general burden of infection?***
  - ***Potentially through mechanisms unrelated to antimicrobial action?***

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Discussion of Recommendations

Animal Studies
-

Human/Epidemiologic Studies
- Comprehensive evaluation of multiple infectious organisms in GWI cases vs. controls
  - *L. Tropica*
  - Mycoplasma species
  - Other? *(e.g. sand fly fever, brucella. "gram negative cocci")*

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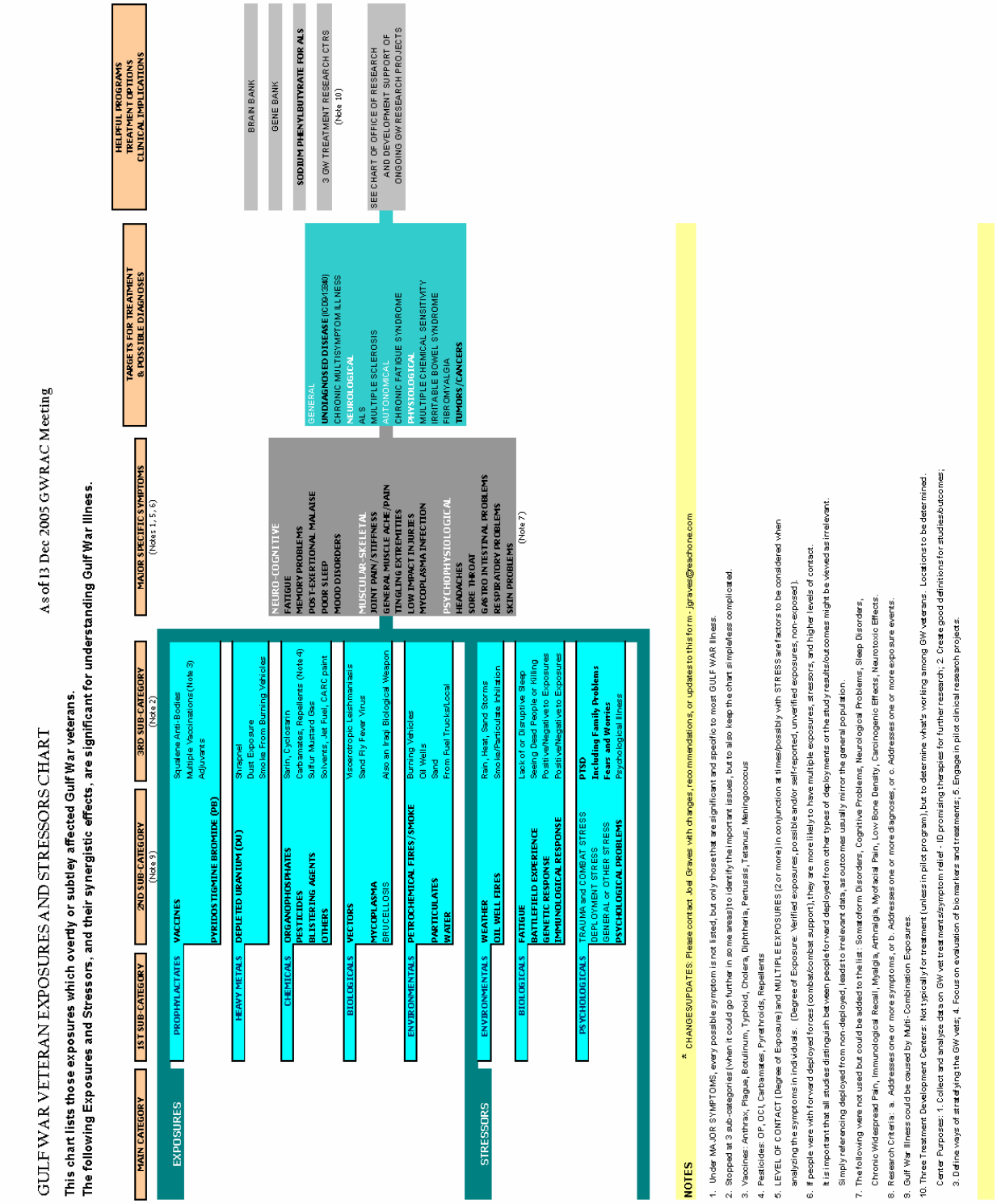
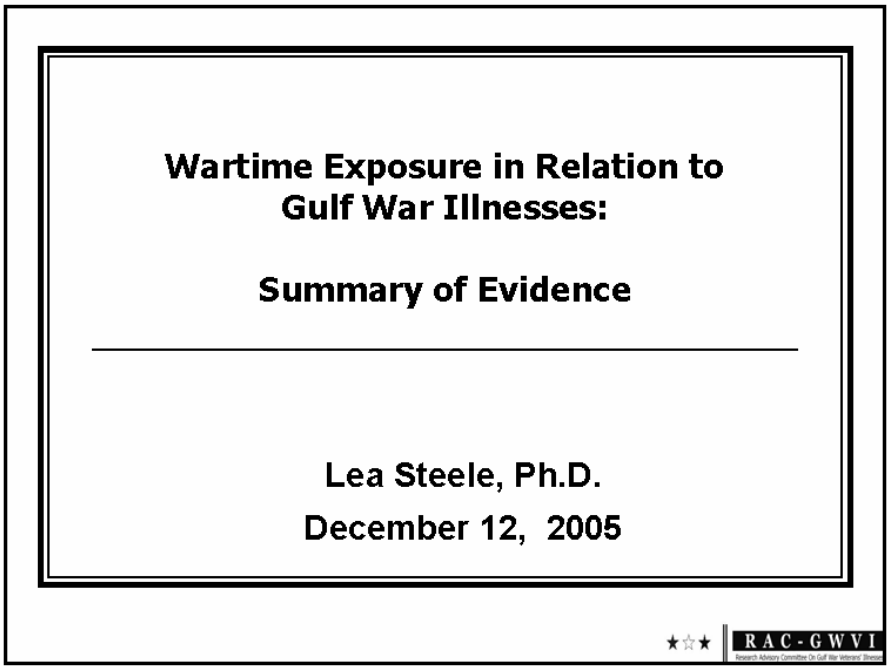
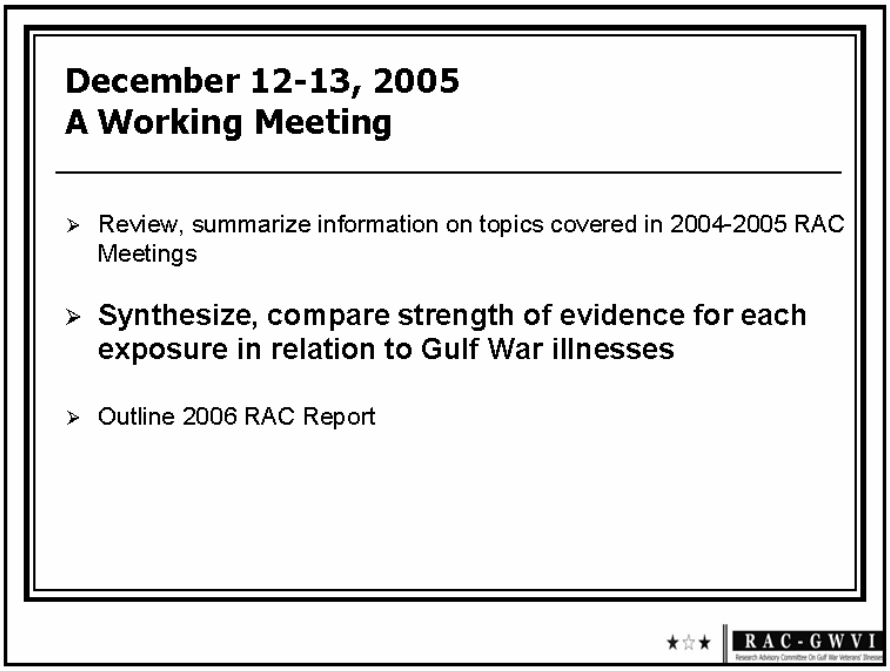
Presentation 6 – Joel Graves



Presentation 7 – Lea Steele





RAC 2006 Report

- Findings, recommendations re: topics reviewed in 2004 and 2005
- Update on topics covered in 2004 RAC Report
- **Synthesis and analysis of findings, identification of research priorities**

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Comparison of evidence re: Exposures

- **Stressful exposures**
- **Chemical weapons**
- **Pesticides/repellants**
- **PB**
- **Vaccines**
- **Depleted uranium**
- **Oil well fires**
- **Tent heaters, combustion products**
- **Particulates**
- **Fuel exposures**
- **Solvents, CARC paint**
- **Infectious diseases**

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Considering the Degree and Weight of Evidence for Gulf War-related Exposures

- Primary interest is likely relationship between exposure and "Gulf War Syndrome" multisymptom illnesses
- In some cases, evidence may suggest association with other health issues

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Considering the Degree and Weight of Evidence for Gulf War-related Exposures

→ Big picture: extent and patterns of exposure during deployment

→ Known toxic effects of exposure

→ Epidemiologic studies of Gulf War veterans

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Rating the Evidence

➔ For all sources of information, consider strength and reliability of methods used

➔ GW epidemiologic research: evaluate strength of findings on key parameters

- Sample *(size, representativeness, etc)*
- Methods, measures
- Statistical analyses

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Statistical Analyses?

➔ Gulf War illness research usually involves:

- *Complex of multiple causal factors*
- *Complex of multiple symptoms in multiple systems*
- *No objective indicators of "disease"*

➔ Some of the most prominent Gulf War epidemiologic studies have great samples and data collection methods, but overly simplistic data analyses

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Important to Consider How Data Were Collected and Analyzed

➔ Overly simple analyses can generate erroneous conclusions about exposures and GWI

➔ Complex exposures require consideration of:

- *Effects of "grouped" exposures*
- *Different risk factors in different subgroups*
- *Effects of combinations of exposures*

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Table 10. Population Studies Assessing Relationships of Multiple Exposures in Theater to Gulf War Veterans' Illnesses

Population Studied	Sample Size	Health Measure	Association with Self-Reported Exposures: Chemical Weapons	PB	Pesticide Use
*Air Guard veterans[232]	1,002	severe CMI	+	+	+
		mild/moderate CMI	+	+	+
*Army veterans from New England, New Orleans[244]	291	neurological and musculoskeletal symptoms	+	--	+
Australian veterans[24]	1,456	functional impairment	+	+	+
Iowa veterans[138]	1,896	cognitive dysfunction	+	+	+
*Navy Seabees[36]	11,868	CMI (modified)	+	+	+
*Navy construction battalion[107]	249	1 or more of 3 defined syndromes	+	+	+
*New England Army veterans[301]	1,290	CMI (modified)	na	+	na
*Pacific Northwest veterans[201]	354	unexplained illness	--	+	+
UK male veterans[349]	2,735	CMI (modified)	+	+	+
*UK veterans[52]	7,971	symptom severity	na	+	+

CMI: chronic multisymptom illness as defined by Fukuda et al.[93]
+ : statistically significant association; -- : association not statistically significant; na: association not assessed
* Indicates analyses controlled for possible confounding due to concurrent exposures

Comparison of evidence re: Exposures

- Psychological stressors related to deployment
- Chemical weapons
- Pesticides/repellants (various)
- PB
- Vaccines
- Depleted uranium
- Oil well fires
- Tent heaters, combustion products
- Particulates
- Fuel exposures
- Solvents, CARC paint
- Infectious diseases

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Gulf War Exposures:

Summary Areas of Consideration

➔ Big picture re: extent and patterns of exposure

➔ Known toxic effects

➔ GW epidemiologic studies

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Psychological Stressors During Deployment

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Psychological Stressors Associated with Gulf War Deployment

- ➔ Big picture: exposures
- ➔ Known toxic effects
- ➔ GW epidemiologic studies

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➔Big Picture
Psychological Stressors

- Many types reported, from less severe to extremely traumatic
- How common?
  - Chemical alerts 66 %
  - SCUD exploded nearby 43 %
  - Participation in combat 27 %
  - Witnessed deaths 26 %
  - Family problem 7 %
  - Sexual assault 1 %
- Some more common among ground troops; similar in UK
- Many of these were not unique to 1990-91 Gulf War

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➔Known Toxic/Adverse Effects
Psychological Stressors

- Severe trauma associated with PTSD, other psychiatric conditions
- PTSD, other psych conditions associated with higher levels of s/r somatic symptoms
- Lower–level stressors associated with short-term immune alterations
- Less is known re:
  - Somatic symptoms after trauma in the absence of psych illness?
  - Persistence of somatic symptoms many years after lower-level stressors?

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➔Known Toxic/Adverse Effects Psychological Stressors

- Animal studies have shown that stress can alter effects of other Gulf War-related exposures
  - Can increase adverse effects of PB, DEET, permethrin combinations
  - Effects on blood brain barrier?
  - May modulate neurotoxic effects of DU

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➔Epidemiologic Findings in Gulf War Veterans Psychological Stressors

	Unadj	Adj	*Ref*
Chemical alerts	2.6*	1.2	*GG*
	2.2*		*CU*
	1.9*, 2.7*	ns	*JW*
SCUD exploded nearby	1.6*		*CU*
Participated in combat	2.6*	1.3	*GG*
High combat stress		2.5	*PS*
Witnessed deaths	3.1*	1.3	*GG*
	1.6*		*CU*
Family problem	1.7*	1.6	*RN*
Sexual assault	8.3*		*HK*
"Combat stress index"	p = 0.02	ns	*RH, syn 1*

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➔Epidemiologic Findings Psychological Stressors

- All significantly associated with multisymptom illness in unadjusted analyses, with ORs ~ 1.6 – 3.1
- High crude OR (8.3) for sexual assault in Kang study
- None significant in studies adjusting for other wartime exposures

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Exposure to Chemical Weapons

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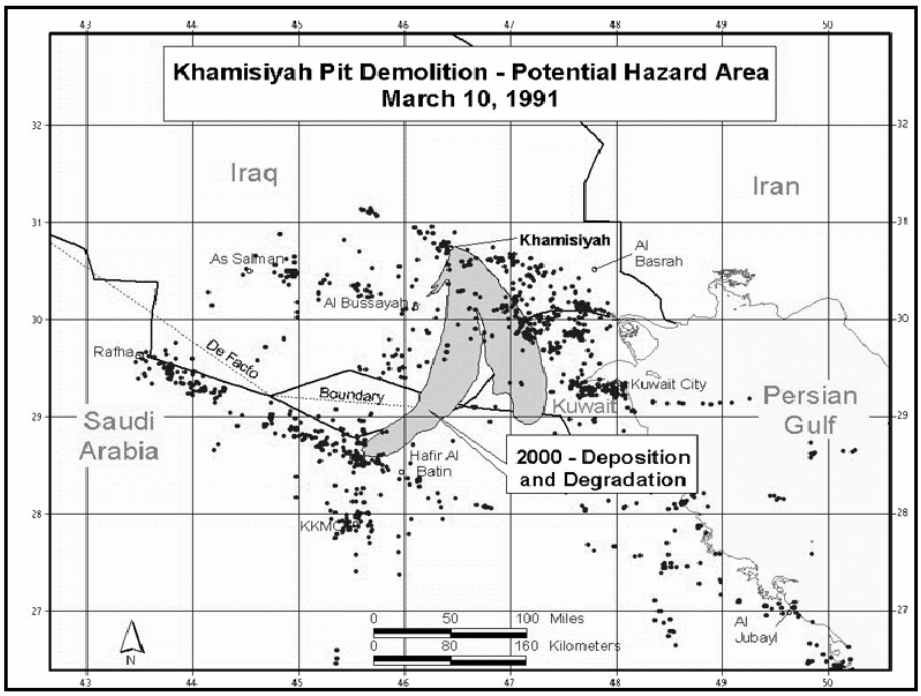
Chemical Weapons

- ➔ Big picture
- ➔ Known toxic effects
- ➔ GW epidemiologic studies



➔Big Picture
Chemical Weapons

- Actual extent of exposure unknown
- OSAGWI report indicates potential for very low-level exposures to ~100,000 following Khamisiyah demolitions
- Multiple reports of other incidents; 80% of chemical targets destroyed
- Self-reported exposures:
  - Chemical alerts 66 %
  - SCUD exploded nearby 43 %
  - CBW 22-24%
  - Chemical warfare agents 5-10%
- More commonly reported by ground troops; similar in UK
- Exposure is fairly unique to 1990-91 Gulf War

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➔Known Toxic Effects Chemical Weapons

- High-level exposures deadly
- Little known re: low-level, chronic effects in humans
  - Japanese studies indicate chronic symptoms, subtle neuro effects in sarin attack survivors
- Animal studies have identified persistent neuro, immune effects following low-level exposures
- Few animal studies have evaluated interaction of sarin with other Gulf War-related exposures

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Table 7. Studies of Chronic Effects of Low-Dose Sarin Exposure in Animals

Study	Year	Animal Model	Major Finding
Burchfiel[44]	1976	monkey	Persistent effects on electroencephalograph readings
Husain[128]	1993	mouse	Delayed development of spinal cord lesions
Jones[149]	2000	rat	Chronic reduction in nicotinic ACh receptor binding in cerebral cortex
Kassa[165]	2000	rat	Chronic alteration in immune function (lymphocyte proliferation, bactericidal activity of macrophages)
Kassa[167]	2000	rat	Persistent changes in DNA and protein metabolism in liver tissues
Kassa[166]	2001	rat	Subtle chronic signs of neurotoxicity and immunotoxicity with repeated exposures
Kassa[161]	2001	rat	Impaired spatial memory
Conn[57]	2002	rat	No persistent effects on reported indices of temperature regulation and motor activity
Henderson[113]	2002	rat	Delayed, persistent changes in cholinergic receptors in brain areas associated with memory loss and cognitive changes
Hulet[126]	2002	guinea pig	Persistent failure to habituate on functional test battery
Scremin[263]	2002	rat	Persistent increase in cerebral blood flow in specific areas
Kalra[151]	2002	rat	Suppression of immune response (antibody-forming cells and T cell responses) mediated by the autonomic nervous system
Roberson[254]	2002	guinea pig	Chronic depression of AChE activity, persistent behavioral changes (disordered activity, increased rearing behavior)
Husain[127]	2003	mouse	Persistent reductions in respiratory exchange, blood AChE activity and BChE activity, NTE activity in various tissues
Scremin[262]	2003	rat	Down-regulation of muscarinic receptors in hippocampus, decreased habituation
Kassa[162-164]	2003 2004 2004	mouse	Chronic alteration in immune function (increase in CD19 cells, decrease in CD4 cells, decrease in mitogen-induced lymphoproliferation, increased NK cell activity)

RAC-GWVI Research Advisory Committee On Gulf War Veterans' Illnesses

➔Epidemiologic Findings in Gulf War Veterans
Chemical Weapons

	Unadj	Adj	Ref
Chemical alerts	2.6*	1.2	*GG*
	2.2*		*CU*
	1.9*, 2.7*	ns	*JW*
Poison gas	6.3*		*JW*
Likely chem attack		7.8*	*RH, syn 2*
Poor prot/chem attack	3.2*		*PS*
In Sector 7 Jan 20		4.3*	*RH, syn 2*
Nerve gas	15.1*		*HK*
Chem/bio weapons	2.5*, 6.0*	2.3*, 3.5*	*RN*
Chemical warfare agents	p<.001		*Iowa*

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➔Epidemiologic Findings
Chemical Weapons

- All CW variables sign. associated with multisymptom illness in unadjusted analyses, with ORs ~ 2.0 – 6.3
- High crude OR (15.1) for "nerve gas" exposure in Kang study
- CW variables (except "chemical alert" questions) are sign. associated with GWI in studies that adjust for other wartime exposures: ORs ~ 2.3 – 7.8
- Brain cancer mortality sign. elevated among veterans in Khamisiyah plume area; few other assoc. with modeled Khamisiyah proximity

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Pesticides, Insect Repellants

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Pesticides, Insect Repellants

- ➔ Big picture
- ➔ Known toxic effects
- ➔ GW epidemiologic studies

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April 2003 Report from DOD Special Assistant for Gulf War Illnesses

Environmental Exposure Report

Pesticides

Environmental Exposure Reports are reports of what we know today about certain events of the 1990-1991 Gulf War. This particular environmental exposure report focuses on the use of pesticides by US military personnel and the resulting exposures to these compounds. Our goal is, to the extent possible, to determine if the pesticides used during the Gulf War contributed to unexplained illnesses reported by some Gulf War veterans. This is an interim, not a final, report. We hope that you will read this and contact us with any information that would help us better understand the events reported here. With your help, we will be able to report more accurately on the events surrounding pesticide use and exposures. Please contact my office to report any new information by calling:

1-800-497-6261

Dale A. Vesser
Acting Special Assistant for Gulf War Illnesses, Medical Readiness, and Military Deployment
Department of Defense

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➔Big Picture
Pesticide Exposures

- Multiple compounds used; DOD-identified 37; 15 of possible concern
- Diverse applications: skin, uniforms, tents, bedding, area fogging, delousing
- OSAGWI report indicates 41,000 potentially overexposed to pesticides
- Studies indicate highly correlated use of multiple pesticides, i.e., those who used high levels of one pesticide most likely to use higher levels of others
- RAND study found higher pesticide use correlated with higher PB use

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➔Big Picture
Pesticide Exposures

- Self-reported exposures:
  - Insecticide spray 35%
  - Insect repellant 28-35%
  - Personal pesticides 48%
  - Insecticide cream/spray 26-28%
- More commonly reported by ground troops; Reserve/Guard use may be higher than Active
- Similar usage in UK
- Levels, pattern of use unique to 1990-91 Gulf War?

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➔Known Toxic Effects
Pesticides

- Acute poisoning produces diverse symptoms, delayed neuro syndrome
- Large body of toxicological research on adverse effects of different compounds on multiple systems
- Community and occupational studies indicate chronic, low level exposures associated with higher symptom levels
- Animal studies demonstrate synergistic effects of DEET, OP, and permethrin
- Genetic variation (PON1, BCHE, NTE) linked to individual susceptibility to pesticide exposures

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➔Epidemiologic Findings in Gulf War Veterans
Pesticides

	Unadj	Adj	Ref
Pesticides	3.5* 2.2*	1.9*	GG CU
Flea collar	3.8*	1.3 8.7*	GG RH, syn 1
Treated uniform	3.4* 3.6* 1.9*	1.2	GG PS CU
Insect repellant	1.9*, 3.4* 3.3*	1.7*, 2.4* ns	RN PS
Pesticides	p<.001* p<.001*	p<.001*	SP;n+ms IA, all
Insect repellant > 14 days	p<.001*	p<.001*	NC
Amt skin repellant	p<.001*	p<.001*	RH, syn 3

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➔Epidemiologic Findings
Pesticides

- All pesticide variables sign. associated with multisymptom illness in unadjusted analyses, with ORs ~ 1.9 – 3.8
- Pesticide variables are sign. associated with GWI in studies that adjust for other wartime exposures (except 2 variables in Navy Seabee study, 1 in NW vets): ORs ~ 1.7 – 8.7
- Some evidence of dose-response relationship
- "Handling of pesticides" sign. associated with non-disease related mortality in UK veterans

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NAPP Pills (Pyridostigmine Bromide)

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Pyridostigmine Bromide

➔ Big picture

➔ Known toxic effects

➔ GW epidemiologic studies

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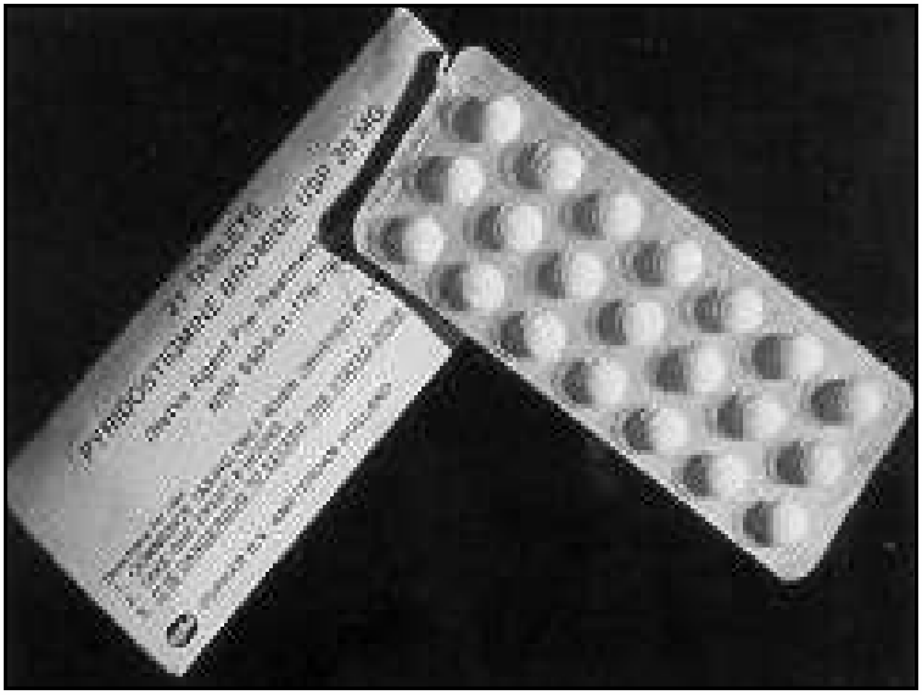

➔Big Picture
PB Exposures

- Orders to use and implementation varied by unit; commander discretion
- Recommended use: 3 x 30 mg tables per 24 hour period
- RAND study indicates use varied widely; higher pesticide use correlated with higher PB use

➔Big Picture
PB Exposures

- Self-reported exposures:
  - Used PB 49 - 60%
  - Seabees study 32%
  - Used NAPS > 14 days 60% (UK)
- More commonly reported by ground troops; Guard use may be higher than active
- Similar usage in UK
- Exposure to PB unique to 1990-91 Gulf War

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➔Known Toxic Effects
PB

- Used for many years to treat myasthenia gravis, considered safe in clinical use
- Acute side effects (mostly GI) reported to have affected about 1/3 with PB use during the Gulf War
- Animal studies indicate synergism with DEET, permethrin
- Preliminary evidence of PB causing severe difficulty for individuals with low BChE activity

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➔Epidemiologic Findings in Gulf War Veterans
PB

	Unadj	Adj	Ref
Took PB tablets	3.0*	1.5*	*GG*
	1.4*		*Aust*
	1.4*, 3.0*	1.6*, 2.9*	*RN*
	2.6*		*CU*
	ns	ns	*SP*
Took 1-21 PB pills	1.9*, 2.3*	1.4	*JW*
22 + PB pills	2.5*, 3.7*	2.1*	
Took > 21 PB tablets	4.44*	2.2*	*PS*
No. of days took NAPs		p<.001*	*NC*
Side effects from NAPs		p<.001*	*NC*
Advanced PB side effects	p<.001*	p<.001*	*RH syn2,3*
Used PB	p<.001*		*Iowa*

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➔Epidemiologic Findings
PB

- PB variables sign. associated with multisymptom illness in unadjusted analyses, with ORs ~ 1.4 – 4.4
  (1 exception: 1st Ft. Devens study)
- PB variables sign. associated with GWI in studies that adjust for other wartime exposures, ORs ~ 1.7 – 8.7
  (not in Ft. Devens study or at lower level in 2nd Ft. Devens study)
- 3 studies indicate a dose/response effect
- 2 studies support association with acute side effects of PB

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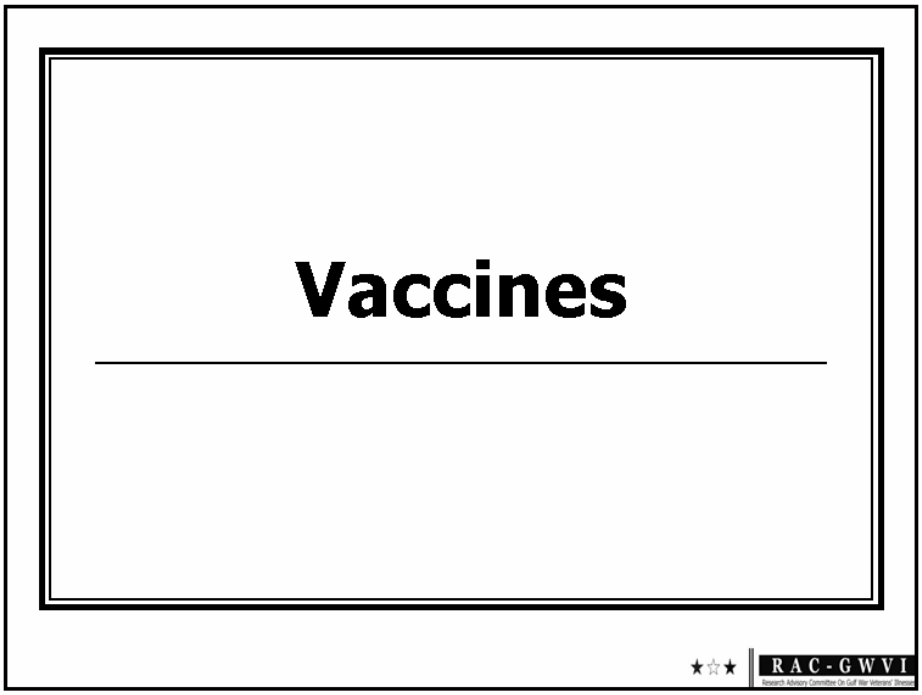
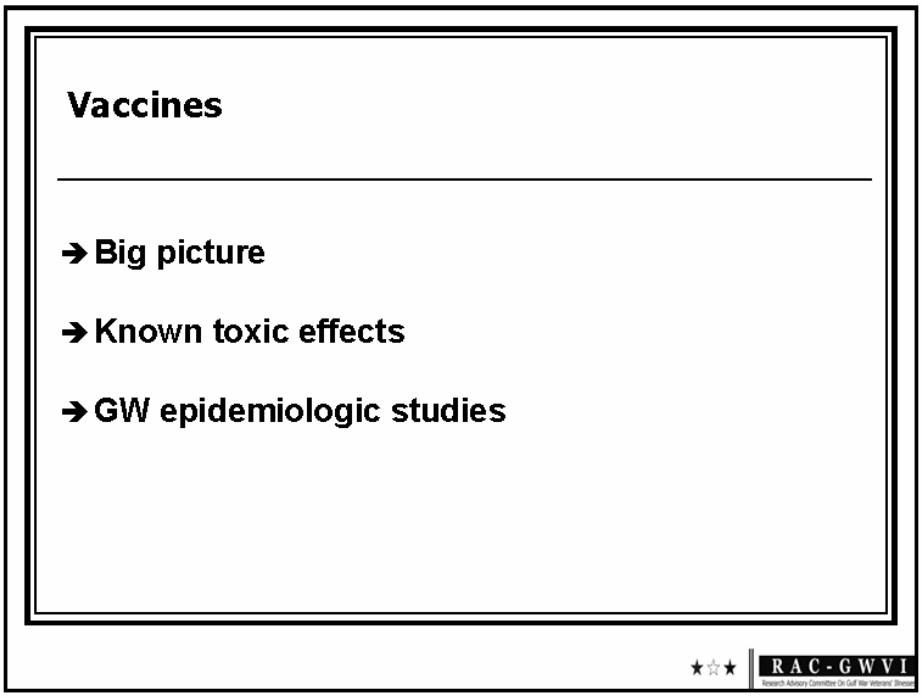

Vaccines
★☆★
RAC-GWVI


Vaccines
➔ Big picture
➔ Known toxic effects
➔ GW epidemiologic studies
★☆★
RAC-GWVI

➔Big Picture
Vaccines

- Self-reported exposures:
  - Anthrax 41%
  - Typhoid 44%
  - Botulinum 3%
  - Plague 15%
  - Meningococcus 6%
  - 10 shots or more 34%
- Combat troops reported most likely to have received anthrax, botulinum toxoid

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➔Epidemiologic Findings in Gulf War Veterans
Individual Vaccines

	Unadj	Adj	Ref
Botulinum	1.8*		KB
	4.9*	1.4	GG
Meningococcus	1.6		
	3.0*	1.3*	GG
Anthrax	1.5*, 1.9*	1.5*	JW
	1.7*		KB
	3.7*	1.0	GG
	1.3		MH(post)
	1.5*	0.9	CU
Plague	1.3		KB
	3.2*	0.9	GG
	0.9		MH(post)
	1.3*		CU

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➔Epidemiologic Findings in Gulf War Veterans
Number of Vaccines

	Unadj	Adj	*Ref*
Post deploy:			
0-1	1.0		
2	2.2*		*MH*
3	2.4*		
4	2.2*		
5+	5.0*		
Symptom score/# vaccines		p<.001	*NC*
0	1.0		*Austr*
1-4	0.9		
5-9	1.3*		
10+	1.2*		

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➔Epidemiologic Findings
Vaccines

- Unadjusted analyses: variable results for individual vaccines
  anthrax: 4 positive (OR ~1.5-3.7); 1 neg
  botulinum: 2 positive (OR~1.8-4.9); 0 neg
  plague: 2 positive (OR~1.3-3.2); 2 neg
- Very few studies have looked at vaccine-associated risk while controlling for effects of other exposures in theater
  anthrax: 1 pos (OR = 1.5); 1 neg
  mening: 1 pos (OR = 1.3)
  plague: 1 neg
- Number of vaccines: Only UK and Australia studies
  2 studies show positive association without adjusting for other exposures:
  Cherry study found positive association in adjusted analysis (p<.001)

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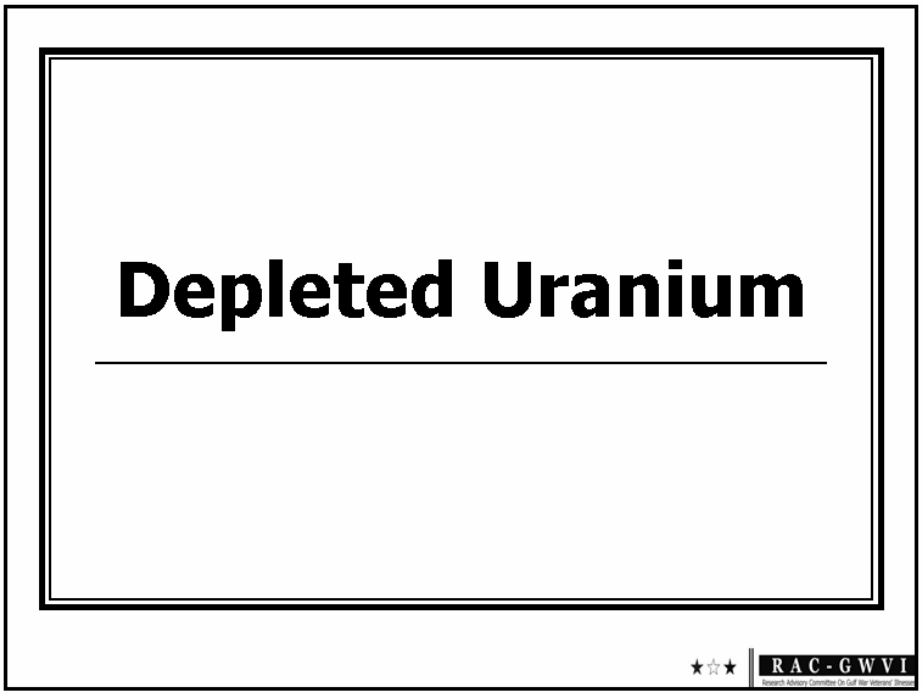
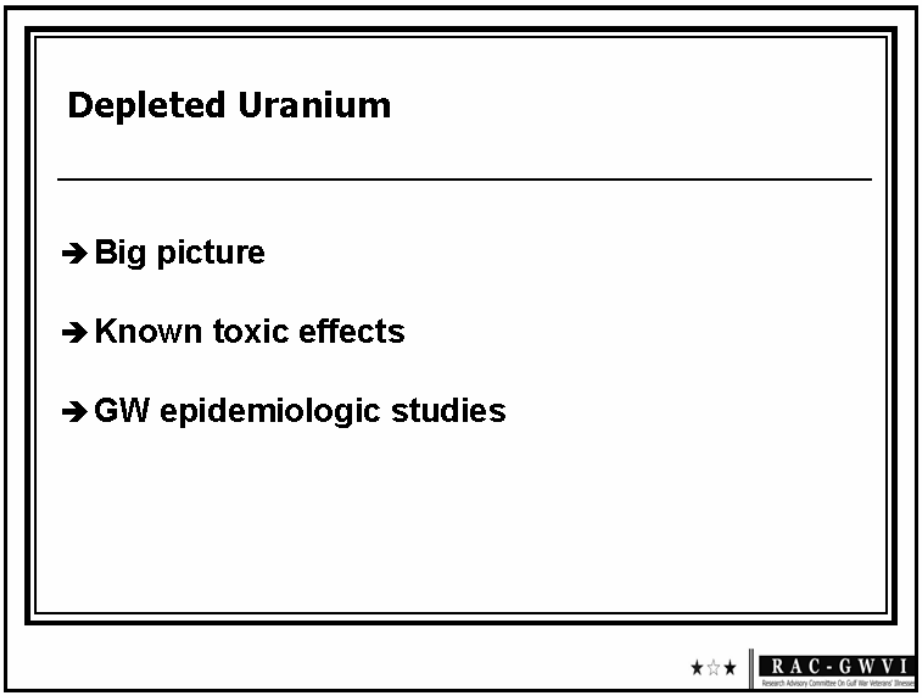

Depleted Uranium
RAC-GWVI


Depleted Uranium
➔ Big picture
➔ Known toxic effects
➔ GW epidemiologic studies
RAC-GWVI

➔Big Picture
Depleted Uranium

- No clear estimate of total number exposed
- Small cohort with shrapnel, larger number exposed by inhalation
- Self-reported exposures low, problematic question in epi studies
  - Kang 10%
  - Wessely 10%
  - Gray 2%
- DU also used in Kosovo, current deployments

★☆★ RAC-GWVI

➔Epidemiologic Findings in Gulf War Veterans
Depleted Uranium

	Unadj	Adj	*Ref*
Depleted uranium	ns		*RH (all syn)*
	4.5*		*PS*
	2.3		*Dan, neuro*

.
.

★☆★ RAC-GWVI

➔Epidemiologic Findings Depleted Uranium

- Very few epidemiologic studies have looked at DU exposures
- Those that did didn't solicit information likely to be reflective of actual DU exposures
- VA DU cohort (Baltimore study) does not report results re: symptoms, multisymptom illness

★☆★ RAC-GWVI

Oil Well Fires

★☆★ RAC-GWVI

Oil Well Fires

- ➔ Big picture
- ➔ Known toxic effects
- ➔ GW epidemiologic studies

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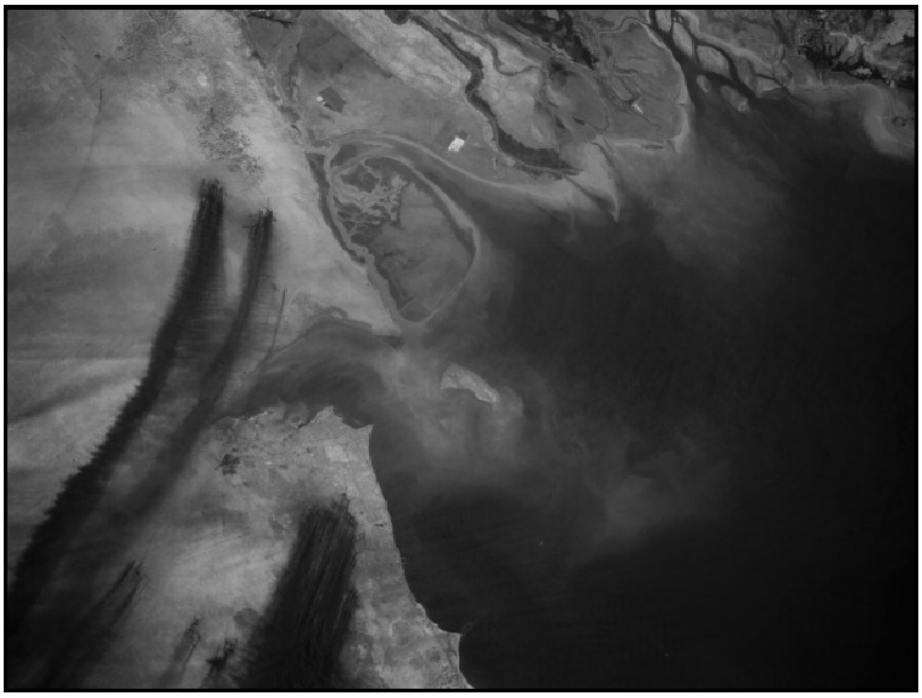

➔Epidemiologic Findings in Gulf War Veterans
Oil Well Fires

	Unadj	Adj	Ref
s/r Oil fire smoke	1.9*, 3.4*	1.3, 1.5	*RN*
	1.8*		*CU*
	2.2*	1.2	*GG*
Modeled oil fire smoke	1.5*	0.4	*GG*
Odor from burning wells		2.1*	*JW*
Consumed food cont w/oil	10.6*		*HK*
Eye irr/ smoke: 1-5 days 6+days	2.64* 4.47*		*PS*
Number days exposed		p<.001*	*NC*
Smoke, combustion	p<.001*		*Iowa*

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➔Epidemiologic Findings
Oil Well Fires

- All variables sign. associated with multisymptom illness in unadjusted analyses, with ORs ~ 1.5-4.5
- Oil well fire variables sign. associated with GWI in 2 studies that adjust for other wartime exposures OR = 2.1
  Not sign associated in Seabees study, Air Guard study
- 3 studies suggest dose/response effect
- Kang neuro factor sign associated with oil-contaminated food (OR=10.6)
- No association in study that used modeled exposure to smoke
  (Seabees study)

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Exposures: Questions to Consider

What evidence is there re: the potential for "Exposure X" to have contributed to the chronic symptoms affecting Gulf War veterans?

- *Potential role as a single exposure?*
- *Potential role in combination with other exposures?*
- *Potential for a subset of individuals to have been particularly affected due to their location or occupation?*
- *Potential for some individuals to have greater susceptibility to this exposure?*

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Exposures: Additional consolidation of information

- *More detailed breakdown where possible, e.g. pesticide types and combinations*
- *Calculate attributable risk where possible*
- *Compare findings from different studies: how are they similar? how are they different?*
- *Patterns related to branch of service, location, types of case definitions, exposure questions?*

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Gulf War Exposures in relation to GWI: Preliminary Summary of Epidemiologic Evidence

	Unadj	Adj	Adj Results Consist	Dose/ resp	S/R variable
Psychological stressors	1.6-3.1	ns	yes	-	
Chemical weapons	1.9-6.3	2.3-7.8	yes	-	↓
Pesticides	1.9-3.8	1.7-8.7	yes	yes	
NAPP/PB pills	1.4-4.4	1.5-2.9	yes	yes	+
DU	4.5*	no studies	-	-	↓
Oil well fires	1.8-4.5	2.1	no	yes	+
Vaccines: anthrax meningococcus	1.5-3.7 3.0	1.5 1.3	little info	-	↓
Number of vaccines	3 sign	1 sign	little info	yes	?

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Gulf War Exposures in relation to GWI: Preliminary Summary of Evidence

	Known Toxic Effects: Possible Relation to GWI?		Evidence of synergism w/other GW exposures?
	Human/ Occup	Animal	
Psychological stressors	yes	yes	yes
Chemical weapons	~	yes	
Pesticides	yes	yes	yes
NAPP/PB pills	?		yes
DU	?	yes	yes
Oil well fires	no	?	?
Vaccines: anthrax	?	?	?
Number of vaccines	no	?	?

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Gulf War Exposures in relation to GWI: Preliminary Summary of Evidence

	Pattern of Exposure Compatible with Patterns of GWI?	
	Higher in ground troops?	Greater exp in 1990-91 PGW?
Psychological stressors	yes	no
Chemical weapons	yes	yes
Pesticides	yes	?
NAPP/PB pills	yes	yes
DU	yes	no
Oil well fires	yes	yes
Vaccines: anthrax	yes	no
Number of vaccines	no	no

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Gulf War Exposures in relation to GWI: Summary of Epidemiologic Evidence

Psych stressors	Evidence consistently indicates not associated
Chemical weapons	Two studies support sign association, higher OR with more severe illness; s/r exposure problematic
Pesticides	Consistent sign assoc, dose response
NAPP/PB pills	Consistent sign assoc, dose response
DU	Almost no useful information
Oil well fires	Results inconsistent, may relate to proximity/duration
Vaccines, individual	Very little clear information; s/r problematic, little control for confounding
Number of vaccines	Little info, 1 strong study suggests association

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Exposures and GWI: Preliminary Conclusions Strongest Evidence

- Strongest evidence from epidemiologic studies supports pesticides and PB as causal factors in GWI
  - Animal studies support plausibility, especially when PB combined with other compounds
  - Overall pattern of exposures also support association
- Two studies support positive associations with chemical weapons, but s/r exposure questionable in one
  - Unknown if exposures extensive enough to explain large proportion of cases
  - Brain cancer/Khamisiyah findings could be due to nerve agents, confounding by other exposures?

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Exposures: Preliminary Conclusions Little/Poor Evidence

- Very little useful information concerning likely associations between vaccines and GWI
  - Significant associations generally modest
  - Little animal or human research informs plausibility
- Almost no information concerning likely associations between DU and GWI
  - Animal studies suggest possible neuro effects
  - Unknown if similar conditions seen in other deployments with comparable DU exposures

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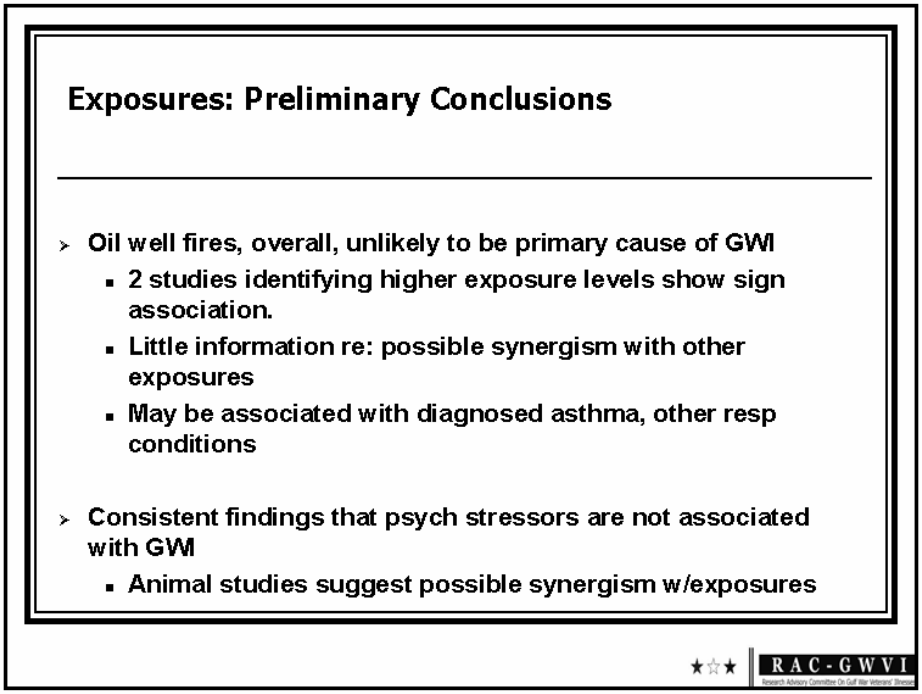

Exposures: Preliminary Conclusions
Oil well fires, overall, unlikely to be primary cause of GWI
2 studies identifying higher exposure levels show sign association.
Little information re: possible synergism with other exposures
May be associated with diagnosed asthma, other resp conditions
Consistent findings that psych stressors are not associated with GWI
Animal studies suggest possible synergism w/exposures
RAC-GWVI

Presentation 8 – Joel Kupersmith

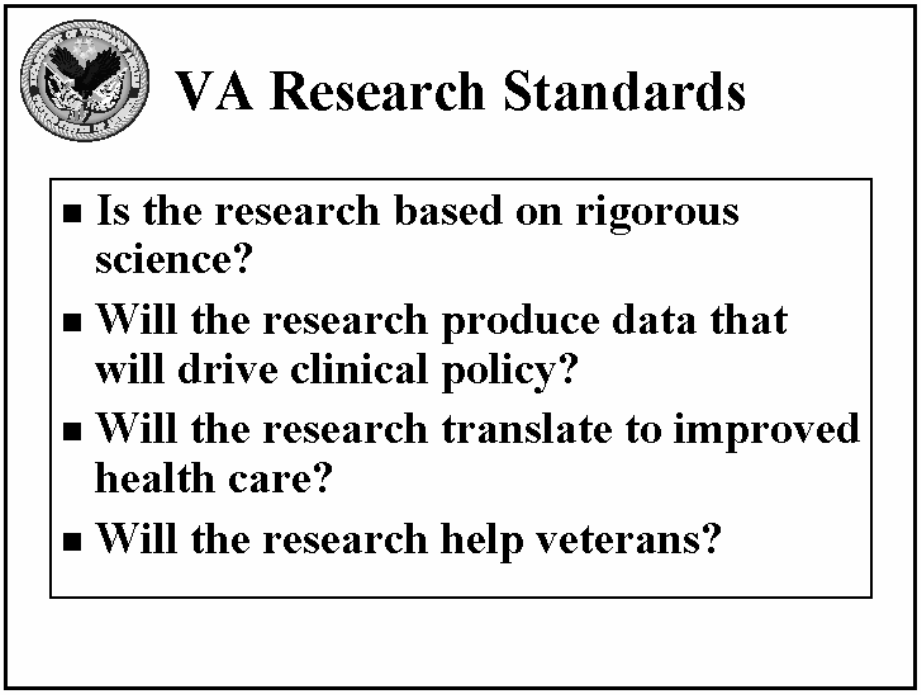
Gulf War Update

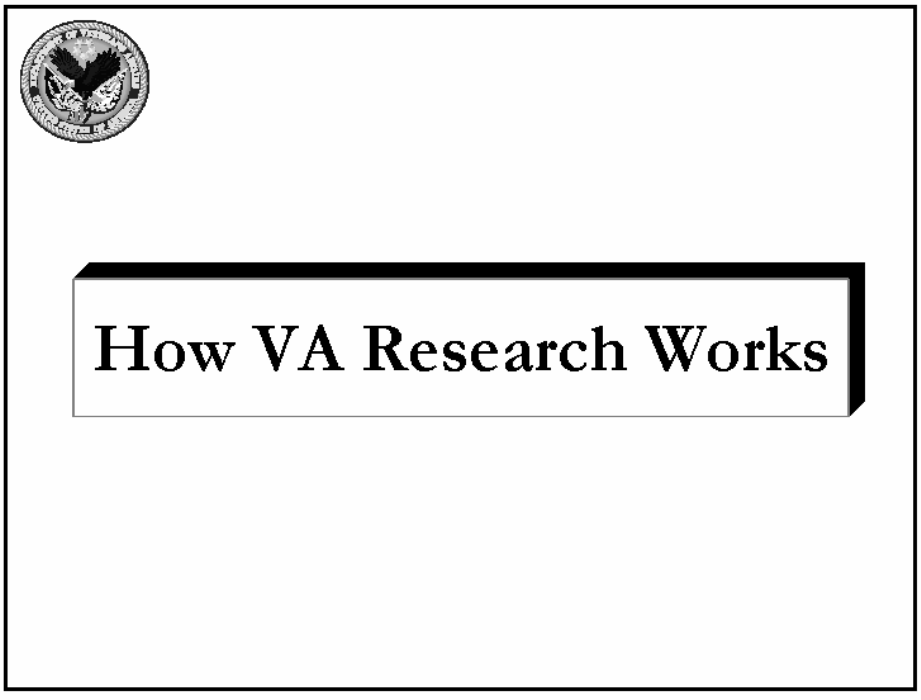
Joel Kupersmith, MD
Chief Research & Development Officer
Veterans Health Administration
Department of Veterans Affairs
December 13, 2005

VA Research

Our mission is clear and Congressionally-mandated :

*"To discover **knowledge** and create innovations that advance the health and care of veterans and the nation."*


VA Research Standards
Is the research based on rigorous science?
Will the research produce data that will drive clinical policy?
Will the research translate to improved health care?
Will the research help veterans?


How VA Research Works

Intramural Research Program

- VA Research is an intramural program.
- Researchers must be employed by VA (5/8s or more in most cases).
- Unlike agencies such as the NIH or DoD, VA has ***no*** statutory authority to make research grants to colleges and universities, cities and states, or any other non-VA entity.

Organization of VA Research

- Four research services with the VA Office of Research and Development (ORD)
  - Biomedical Laboratory R&D Service (BLR&D)
  - Clinical Science R&D Service (CSR&D)
  - Health Services R&D Service (HSR&D)
  - Rehabilitation R&D Service (RR&D)

Types of Research Sponsored

- Investigator-Initiated Research (Merit Review)
- Mentored Research (Career Development)
- Large-scale, multi-site clinical trials (Cooperative Studies Program)
- Centers of Excellence (all Services)
- Service-Directed Research
- Special Initiatives (e.g., Gulf War Illnesses Research)

Merit Review

- Merit Review
  - Our core business
  - Must produce excellent science
  - Process must be sacrosanct
  - Must be absolutely fair (especially in view of history)
  - Must have uniformity in procedures
  - New initiative - NIH eRAs Computerized system
    - ✓ Will revolutionize system and also promote uniformity

Current ORD Leadership

■ CRADO	Joel Kupersmith
■ Deputy CRADO	Joe Francis (acting)
■ Director, BLR&D	Timothy O'Leary
■ Director, CSR&D	Timothy O'Leary
■ Director, RR&D	Robert Ruff (acting)
■ Director, HSR&D	Shirley Meehan (acting)

Recent Developments

Merit Review FY2005

FY 2005 RFP Merit Review

- 67 Notifications of intent to submit received
- 44 Proposals submitted (~66%)
- Proposals assigned to 2 Subcommittees
- Reviewed on Sept. 16 and Sept. 30
- 12 Proposals Selected for Funding
- Funding expected to begin January 1, 2006

Developing an RFP
The Vetting Process

- Initial Draft(s) of the RFP
- ORD Concurrence Process → Final Version
- VACO Concurrence Process
- RFP Announcement (E-Mail and Web Site)
- LOI/Notice of Intent to Submit
- Proposal Submission (≥ 60 days)
- Reviewer Recruitment/Review (30-60 days)
- Funding Decisions
- Compliance Documentation (30-60 days)
- Funds Released

Funded Proposals

- Exposures
  (10 submitted)
  - Proteomic Analysis of Cellular Response to Biological Warfare Agents (PB, DEET, permethrin)
  - Direct Delivery of Neurotoxins to the Brain by an Intranasal Route (PB, DEET, permethrin)
  - Behavior of Neural Stem Cells in a Rat Model of GWS (PB, DEET, permethrin)
- Brain and Nervous System Function
  (15 submitted)
  - Integrated Neuroimaging and Neuropathological Analysis of the Effects of Physical Activity on Progression and Therapy in ALS
  - Autonomic Functions of Gulf War Veterans with Unexplained Illnesses
  - Motor Neuron Function of Gulf War Veterans with Excessive Fatigue

Funded Proposals

- **Immune Function and Infectious Diseases**
  (5 submitted)
  - **Mechanisms of Immune Dysfunction in Gulf War Illness**
  - **The Diagnosis and Pathogenesis of Occult Leishmaniasis**
- **Symptoms and General Health**
  (14 submitted)
  - **Tissue Factor and Gulf War-Associated Chronic Coagulopathies**
  - **Effect of Hyperthermic Exposure on Susceptibility to Experimental Lung Injury**
  - **Profile of GW Veterans who Applied for Undiagnosed Illness Compensation**

Initiatives for FY2006

New Initiatives for FY 2006

- **Gulf War Treatment Research Center RFP**
  - **Currently in Concurrence**
  - **Up to 3 to be selected for July 1 finding**
  - **$1 million/year (each center)**
  - **Collaboration/Pilot Project with UT Southwestern**

New Initiatives for FY 2006

- **Brain Bank to include ALS and non-ALS (control)**
- **Genetic risk factors and predispositions**
  - **DNA Bank for Gulf War**
  - **Dr. Kang's samples**
    - ✓ **Will need re-consent**

New Initiatives for FY 2006

- **New Merit Review RFP – Jan or Feb release**
  - **Topic Suggestions from RAC-GWVI**

Gulf War Update

Joel Kupersmith, MD
Chief Research & Development Officer
Veterans Health Administration
Department of Veterans Affairs
December 13, 2005

Presentation 9 – William Goldberg

GULF WAR UPDATE

William J. Goldberg PhD
Portfolio Manager
Gulf War Research
Veterans Health Administration
Department of Veterans Affairs

PORTFOLIO CRITERIA

CRITERIA

(with examples)

- **Studies of chronic multisymptom illnesses (CMI) affecting GW veterans and the general population**
  - **Case definitions of CMI affecting Gulf War veterans**
    - Evaluation of Stress Response Systems in Gulf War Veterans with CMI
      (Autonomic system and neurohumoral dysregulation in Gulf War veterans)
    - Autonomic Functions of Gulf War Veterans with Unexplained Illnesses **
      (Autonomic dysfunction as an underlying cause of unexplained symptoms in GW veterans)
  - **Chronic fatigue syndrome**
    - Tissue Factor and Gulf War-Associated Chronic Coagulopathies **
      (Impaired blood flow and circulation as a cause of cognitive difficulties, somatic pain, fatigue)
    - Pituitary Adrenal Function in People with Fatiguing Illness
      (Neurohumoral dysregulation in Gulf War veterans with fatigue)
    - Mechanisms of Immune Dysfunction in Gulf War Illness **
      (Immune dysfunction as a mediator of persistent illness in both CFS and ill GW veterans)
  - **Fibromyalgia**
  - **Irritable bowel syndrome**
    - Pathophysiology of Irritable Bowel Syndrome in Persian Gulf War Veterans **
      (Treatment of GW veterans with gastrointestinal symptoms)
  - **Multiple chemical sensitivity**

CRITERIA

(with examples)

- **Symptoms occurring with higher prevalence in GW veterans**
  - **Fatigue**
    - Patterns of Microarray Gene Expression in Gulf War Illness
      (Changes in gene expression (biomarkers) in Gulf war veterans with fatigue)
    - Pituitary Adrenal Function in People with Fatiguing Illness
      (Neurohumoral dysregulation in Gulf War veterans with fatigue)
  - **Joint and muscle pain**
    - Functional Imaging of Pain in Veterans with Unexplained Muscle Pain
      (fMRI of Gulf War veterans with musculoskeletal pain)
    - Pain Among Gulf War Veterans: Secondary Analysis of CSP#458 Data
      (Prevalence, distribution and characterization of acute and chronic pain in Gulf War veterans)
  - **Gastrointestinal complaints (dyspepsia, gastritis, diarrhea, etc.)**
    - Characterization of Pain Processing Mechanisms in the Irritable Bowel Syndrome
      (Central nervous system control of gastrointestinal pain)
  - **Cognitive dysfunction (memory, attention, etc.)**
    - Glucocorticoid Responsivity in Gulf War Veterans
      (Positron Emision Tomography (PET) of Gulf War veterans - effects of glucocorticoids on memory)
    - Effects of Stress on Memory: Brain Circuits, Mechanisms and Therapeutics
      (Neurobiological basis of memory and development of new therapies for memory storage and retrieval dysfunction)

CRITERIA

(with examples)

- **Symptoms occurring with higher prevalence in GW veterans**
  - **Sleep disturbances**
    - Cholinergic and Monoaminergic Influences on Sleep
      (Identification of brain circuits that produce wakefulness versus sleep)
  - **CNS disorders (neuroimaging studies, ALS, glioblastoma, etc)**
    - Motor Neuron Function of Gulf War Veterans with Excessive Fatigue **
      (Loss or damage of motor nerve cells in GW veterans with muscle and joint pain, muscle spasm, or fatigue)
    - National VA Amyotrophic Lateral Sclerosis Research Consortium
      (Phase I study of sodium phenylbutyrate (NaPB) as a therapy for ALS)
    - Biomarkers Discovery in ALS
      (Identification of biomarkers for ALS in CSF and serum from Gulf War veterans)
    - Genes, Environment, and Oxidative Stress in Neurodegenerative Disorders
      (Gene-environment interactions in an animal model of ALS)
    - Estimates of Cancer Prevalence in Gulf Veterans Using State Registries
      (Prevalence of cancer (including brain cancers) in Gulf War veterans)
    - Improving a mM-CSF Tumor Vaccine for Established Intracranial Gliomas
      (Development of new therapies for glioblastoma (brain cancer))
    - Structural Magnetic Reasonance Imaging in Gulf War-Era Veterans
    - Effects of Gulf War Illness on Brain Structure, Function and Metabolism: MRI/MRS at 4 Tesla

CRITERIA

(with examples)

- **Health effects of potentially hazardous substances, to which GW veterans may have been exposed to**
  - **Pyridostigmine bromide**
  - **DEET**
  - **Permethrin**
    - Proteomic Analysis of Cellular Response to Biological Warfare Agents **
      (response of human cells to PB, DEET, permethrin, and/or anthrax vaccine)
    - Direct Delivery of Neurotoxins to the Brain by an Intranasal Route **
      (Effects of pyridostigmine bromide, DEET, and permethrin)
    - Neurochemical and Neurobehavioral impact of Pyridostigmine Bromide Treatment and Stress
      (Interaction of physiologic stress and PB exposure on acetylcholinesterase)
  - **Oil well fire smoke**
  - **Petroleum products (e.g., jet fuels) and combustion products**
  - **Multiple vaccinations**

CRITERIA
(with examples)

- Other topics from the 21 research questions
  - **Prevalence of altered immune function or host defense**
    - Mechanisms of Immune Dysfunction in Gulf War Illness **
      (Immune dysfunction as a mediator of persistent illness in both CFS and ill GW veterans)
    - T Cell Responses to Multiple Immunizations and Stress
      (Effects of multiple immunizations on immune function)
  - **Exposure to, and prevalence of, leishmania tropica**
    - The Diagnosis and Pathogenesis of Occult Leishmaniasis **
    - Vaccination Against Visceral Leishmaniasis with a multi-epitope vaccine
  - **Physiological responses to biological stress**
    - Effect of Hyperthermic Exposure on Susceptibility to Experimental Lung Injury **
      (Effects of stressful conditions on the ability to respond to subsequent stress, infection or injury)
  - **Likelihood/prevalence of experiencing non-specific symptoms and symptom complexes**
    - Profile of GW Veterans who Applied for Undiagnosed Illness Compensation **

PROGRESS ON FY 2004 RECOMMENDATIONS

STATUS REPORT

- **Finding 2: Treatments that improve the health of veterans with Gulf War illnesses are urgently needed**
- **Committee recommends that the Department of Veterans Affairs (VA) immediately establish a comprehensive program specifically tasked with evaluating treatment-related information and research, and developing data and pilot studies as necessary to identify promising candidate treatments for clinical trials for Gulf War veterans' illnesses**
  - Pathophysiology of Irritable Bowel Syndrome in Persian Gulf War Veterans (Treatment of GW veterans with gastrointestinal symptoms)
  - National VA Amyotrophic Lateral Sclerosis Research Consortium (Phase I study of sodium phenylbutyrate as a therapy for ALS)
  - Integrated Neuroimaging and Neuropathological Analysis of the Effects of Physical Activity on Progression and Therapy in ALS (Therapies to reduce the severity of symptoms in an animal model of ALS)
  - Gulf War Treatment Research Centers (up to 3 to begin funding in FY 2006)

STATUS REPORT

- **Finding 3: A growing body of research indicates that an important component of Gulf War veterans' illnesses is neurological in character**
- **Expand research efforts that utilize magnetic resonance spectroscopy as well as other state-of-the-art neuroimaging technology suited to study brain cell injury and dysfunction …to better characterize differences between ill Gulf War veterans and comparison groups.**
  - Effects of Gulf War Illness on Brain Structure, Function and Metabolism: MRI/MRS at 4 Tesla
  - Structural Magnetic Reasonance Imaging in Gulf War-Era Veterans
  - Glucocorticoid Responsivity in Gulf War Veterans (Positron Emission Tomography (PET) of Gulf War veterans)
- **Develop a comprehensive research strategy designed to evaluate and expand on the growing body of evidence regarding autonomic dysfunction in ill Gulf War veterans**
  - Autonomic Functions of Gulf War Veterans with Unexplained Illnesses (Autonomic dysfunction as an underlying cause of GWVI)
  - Evaluation of Stress Response Systems in Gulf War Veterans with CMI (Autonomic system and neurohumoral dysregulation in Gulf War veterans)

STATUS REPORT

- **Finding 4: Evidence supports a probable link between exposure to neurotoxins and the development of Gulf War veterans' illnesses**
- **Finding 5: A variety of exposures potentially encountered by military personnel in the Persian Gulf theater have been suggested as possible causes or contributors to Gulf War veterans' illnesses. A broad range of Gulf War-related exposures must be thoroughly evaluated as possible contributors to the development of veterans' illnesses.**
- **The Committee recommends … expand research efforts to systematically investigate the chronic effects of exposure to neurotoxins encountered during the Gulf War, including possible chronic effects of combinations of Gulf War-related exposures..**
  - Proteomic Analysis of Cellular Response to Biological Warfare Agents (Effects of pyridostigmine bromide, DEET, and permethrin)
  - Direct Delivery of Neurotoxins to the Brain by an Intranasal Route (Effects of pyridostigmine bromide, DEET, and permethrin)
  - Neurochemical and Neurobehavioral impact of Pyridostigmine Bromide Treatment and Stress (Effects of pyridostigmine bromide)
  - T Cell Responses to Multiple Immunizations and Stress (Effects of multiple immunizations on immune function)

STATUS REPORT

- **Finding 6: Epidemiologic studies have provided preliminary indications that … Gulf veterans may also suffer from elevated rates of diagnosed medical conditions ….**
- **The Committee recommends that rates of medical conditions and disease-specific mortality among Gulf War veterans be regularly assessed and reported, and that studies be undertaken to actively identify veterans with conditions of particular concern. Specifically, VA should:**
- **Identify ALS cases among Gulf War veterans, and evaluate the potential role of toxic exposures encountered in theater or after the war in the development or progression of this disease**
  - National Registry of Veterans with ALS
- **Undertake epidemiologic studies to determine the prevalence of other serious neurological conditions, including multiple sclerosis (MS), Parkinson's disease, and brain cancers, among Gulf War veterans in relation to appropriate comparison groups.**
  - Estimates of Cancer Prevalence in Gulf Veterans Using State Registries
  - Post War Mortality from Neurologic Diseases in Gulf Veterans, 1991-2004 (Prevalence of brain cancer (including glioblastoma) in Gulf War veterans)

STATUS REPORT

- **Finding 10: Overall progress in addressing Gulf War veterans' illnesses has been delayed by the lack of a well-coordinated federal research effort … The Committee therefore recommends that VA**
- … adopt a … research program that … addresses key research questions regarding the nature, causes, and treatments for Gulf War veterans' illnesses, utilizing research solicitations that address specific priority Gulf War illnesses research topics
- … VA should allocate not less than 15 million dollars in each of the next four years in support of a comprehensive and well-managed research portfolio.
- … The program should be directed by a doctoral-level scientist with appropriate expertise in research directly relevant to Gulf War veterans' illnesses.
- Adopt a mechanism for reviewing and funding … proposals that takes into account the relevance of proposed projects to identified Gulf War illnesses research priorities …. Merit review panels should include scientists familiar with … research on Gulf War veterans' illnesses ….
- … regularly review progress on the objectives … to determine which have been adequately addressed, which should be revised, and which require additional follow-through with new and/or more specific funding announcements

ANNUAL REPORT TO CONGRESS

GULF WAR DATABASE

Combined data from VA, DoD, and HHS

GW Research Priorities

- **Symptoms and General Health Status**
  - Q 1: Prevalence of symptoms/illnesses
  - Q 9: More likely to experience non-specific symptoms and symptom complexes?
  - Q 14: More pulmonary symptoms or diagnoses
  - Q 15: Smaller baseline lung function or greater degree of non-specific airway reactivity
  - Q 20: Greater risk of developing cancers of any type
  - Q 21: Higher mortality rate

GW Research Priorities

- **Exposures (Non-Infectious)**
  - Q 3: Exposure concentrations to various petroleum products and combustion products
  - Q 4: Exposure to occupational/environmental hazards
  - Q 5: Exposure to organophosphorus nerve agent and/or sulfur mustard from bombing at Muhammadiyat or weapons bunker at Khamisiyah
  - Q 6: Exposure to chemical agent, other than at Khamisiyah
  - Q 7: Prevalence of pyridostigmine bromide use
  - Q 8: Prevalence of various psychophysiological stressors

GW Research Priorities

- **Brain & Nervous System Function**
  - Q 16: Prevalence of organic neuropsychological and neurological deficits
  - Q 17: Can short term, low level exposures to pyridostigmine bromide, DEET, or permethrin, alone or in combination, cause short-term and/or long-term neurological effects
  - Q 18: Prevalence of psychological symptoms and/or diagnoses
- **Immune Function and Infectious Diseases**
  - Q 2: Exposure to leishmania tropica
  - Q 10: Prevalence of altered immune function or host defense
  - Q 19: Prevalence of leishmaniasis and other infectious diseases

GW Research Priorities

- **Reproductive Health**
  - Q 11: Prevalence of birth defects in offspring
  - Q 12: Lower reproductive success
  - Q 13: Prevalence of sexual dysfunction

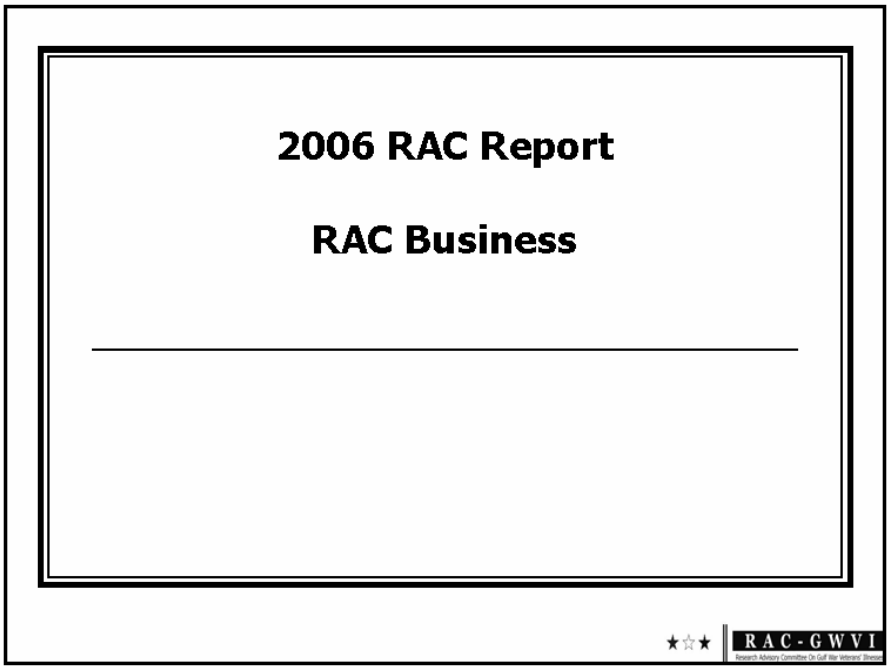
GW Database Coding

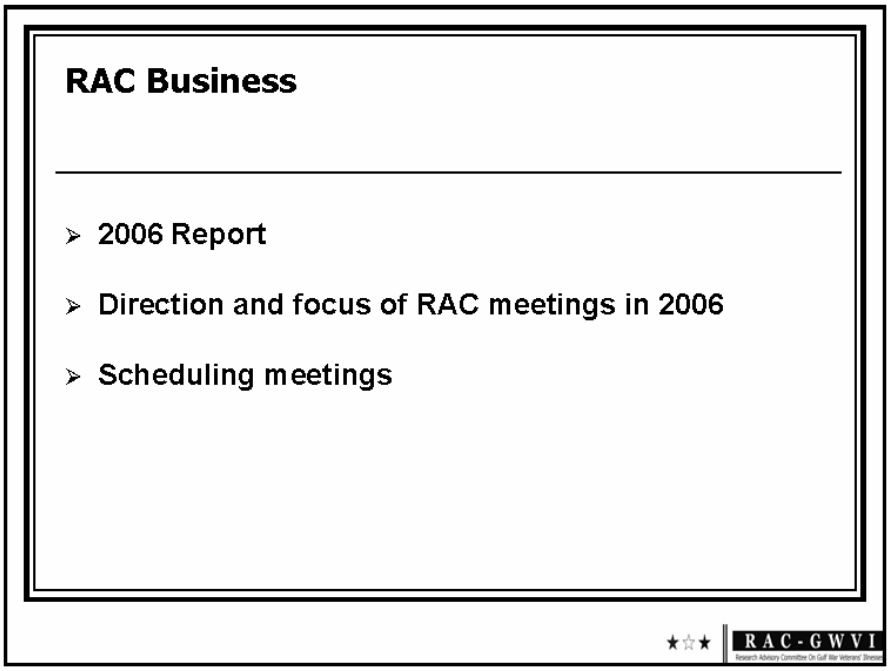
- **Project Type**
  - Clinical
  - Development
  - Epidemiology
  - Mechanistic
- **Focus**

GW Database Coding

- **Focus (new 2-tiered scheme)**
  - Project Focus
    - Diagnosis
    - Exposure
    - Interactions
    - Prevention
    - Symptoms
    - Treatment
  - Research Focus
    - Brain and Nervous System Function
    - Chemical Weapons
    - Exposures (Non-Infectious)
    - Pyridostigmine Bromide
    - Immune Function and Infectious Diseases
    - Reproductive Health
    - Symptoms and General Health

Presentation 10 – Lea Steele





2006 RAC Report

- Findings and recommendations on topics considered in 2004 and 2005

DU	Fuel
Oil well fires	Solvents, CARC
Infectious diseases	Other

- Recent findings re: topics covered in 2004 Report
- Synthesis and analysis of weight of evidence re: exposures and GWI
- Evaluation of VA GWI research program, overall federal effort
- Other?

★☆★ RAC-GWVI

2006 Meetings: New Phase of RAC Activities

- Focus on the basic science of GWI: biological mechanisms that may underlie GWI
  - Promising avenues for identifying biomarkers
  - Implications for treatments
- Examples
  - Chronic neuroinflammatory processes associated with inhaled toxins
  - Neuro-immune-endocrine interactions in chronic multisymptom conditions
  - Pathways and mechanisms of synergistic effects of concurrent exposures
  - Proteomic findings in CSF of veterans with GWI

★☆★ RAC-GWVI

2006 Meetings: New Phase of RAC Activities

- Other ideas/suggestions?

★☆★ RAC-GWVI

Upcoming Meetings: Topics

- "Other Wars": Post-deployment health problems described in military populations
  - *historically*
  - *current deployments*
- Mechanisms

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2006 Meetings

Scheduling

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RAC website: www.va.gov/rac-gwvi

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Appendix B

January 17, 2006, memorandum from Committee to VA ORD

Research Priorities: VA FY2006 Gulf War Illness Request for Proposals
Submitted to VA Office of Research and Development January 17, 2006

Research Advisory Committee on Gulf War Veterans' Illnesses

The Research Advisory Committee on Gulf War Veterans' Illnesses (RAC) is providing the following information in response to a December 13, 2005, request from VA's Office of Research and Development for specific guidance concerning research areas of importance to be identified in VA's 2006 Request for Proposals (RFP) for Gulf War Research.

The following principles and priorities are general in nature, and represent a preliminary summary of Committee recommendations from previous years along with more recent discussions at public meetings. Complete and detailed research findings and recommendations will be finalized and provided to the Secretary later this year in the Committee's 2006 report.

Gulf War Research: Core Research Objectives and Principles

In general, the highest priority Gulf War research studies will address the following objectives:

- Advance efforts to identify beneficial treatments for Gulf War veterans' illnesses either directly by evaluating specific treatments or indirectly by identifying pathophysiological processes potentially amenable to treatments

- Identify measurable differences between symptomatic and healthy Gulf War veterans, particularly specific markers that distinguish individual GWI cases from controls

- Evaluate epidemiologic, clinical, and laboratory parameters in Gulf War veterans stratified into subgroups defined according to exposures, locations, units, or other characteristics potentially associated with the outcome of interest, as opposed to evaluation of all deployed veterans as a single group

- Integrate findings from experimental studies that characterize effects of Gulf War-related exposures with human studies of Gulf War veterans

Studies of Gulf War illnesses should use well-constructed and clearly-described case definitions for Gulf War-associated multisymptom conditions and illness subsets

Proposals whose principal focus is on psychological stress or psychiatric conditions as the primary cause of Gulf War illnesses should not be considered under this RFP.

Priority Gulf War Illness Research Topics

The highest priority Gulf War research studies should address the core objectives previously outlined (i.e., advance knowledge related to treatments, identify objective measures of pathology, evaluate important subsets of Gulf War veterans, and integrate findings in Gulf War veterans with those in experimental studies). Because previous research studies have consistently identified Gulf War-related neurotoxic exposures to be most strongly associated with excess illness in Gulf War veterans, specific research topics of highest priority include:

- Studies that characterize molecular, cellular, systemic, and behavioral effects of individual and combined exposures to neurotoxic substances to which Gulf war veterans were exposed during deployment (e.g., pyridostigmine bromide, low-dose chemical agents, pesticides, insect repellants)

- Comprehensive evaluation of autonomic nervous system function in Gulf War veterans with multisymptom conditions and in illness and/or exposure subgroups

- Epidemiologic studies of rates of diagnosed neurological diseases (e.g., multiple sclerosis, Parkinson's Disease, amyotrophic lateral sclerosis, brain cancer)—as well as CNS abnormalities that are difficult to precisely diagnose—in Gulf War veterans and appropriate comparison groups

- Evaluation of alterations in proinflammatory and inflammatory processes in Gulf War veterans affected by multisymptom conditions; experimental studies that characterize persistent effects of Gulf war-related exposures on proinflammatory and inflammatory processes and their biological mediators in the central nervous system and other target organs

- Studies that investigate biological and genetic variability potentially linked to differences in vulnerability to Gulf War exposures, for example, associations between Gulf War illnesses and genetic polymorphisms and activity levels of enzymes (e.g. paraoxonase, butyrylcholinesterase, acetylcholinesterase) responsible for uptake and metabolism of Gulf War-related neurotoxic exposures

- Studies that utilize new technologies (e.g., proteomic, genomic, and metabolomic methods) capable of characterizing molecular differences between ill Gulf War veterans and healthy comparison groups

- Studies that utilize technologies capable of identifying markers (e.g. retention of toxins, secondary metabolites) that persist after exposure to Gulf War-related compounds individually and in combination

- Use of state-of-the art neuroimaging technologies to characterize aspects of brain structure and function that may distinguish ill Gulf War veterans (including illness/exposure subgroups) from healthy veterans

Gulf War Research: Other Topics of Importance

- Epidemiologic research utilizing a sample size sufficient to evaluate health outcomes of interest (e.g., rates of symptoms and multisymptom conditions, cancer, reproductive effects) among Gulf War veterans known to have been exposed to depleted uranium in comparison to veterans not exposed to depleted uranium during deployment

- Studies of chronic symptoms and health characteristics of military personnel known to have received individual and combinations of vaccines administered to 1990-91 Gulf War veterans, particularly studies of Gulf War-era veterans for whom reliable vaccine information is available

- Studies of veterans with Gulf War illnesses that evaluate clinical, laboratory, and treatment findings associated with multisymptom conditions in the general population (e.g. fibromyalgia, chronic fatigue syndrome, multiple chemical sensitivity, irritable bowel syndrome), including comparisons between Gulf War illnesses and these conditions

- Experimental studies that characterize molecular, cellular, systemic, and behavioral effects of compounds to which Gulf war veterans were exposed (e.g., individual and multiple vaccine combinations, depleted uranium, oil fire smoke, jet fuel) individually, and in combination with other exposures of potential concern

- Comprehensive evaluation of immune parameters among Gulf War veterans with multisymptom conditions, including parameters that may differ among illness and/or exposure subgroups

- Use of diverse methods, including serological testing, polymerase chain reaction testing, and lymphocyte challenge tests, to determine whether Gulf War veterans with multisymptom conditions are affected by undetected infectious conditions (e.g. leishmaniasis, mycoplasma fermentans)

- Use of innovative study designs to evaluate risk of specific types of birth defects or other conditions previously suggested to be elevated among children of Gulf war veterans

- Additional utilization of available epidemiologic and clinical data to more clearly characterize associations between illnesses affecting Gulf War veterans and reported or modeled exposures, using analytic methods capable of distinguishing effects of multiple concurrent exposures and combinations of exposures

- Studies of chronic symptoms and other health characteristics of populations known to have been exposed to chemical weapons